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CONTENTS

INTRODUCTION 1

THE BRITISH PHARMACOPŒIA 2

NAMES, CHARACTERS AND COMPOSITIONS OF DRUGS . 4

DOSES AND PREPARATIONS OF DRUGS 7

ACTIONS AND USES OF DRUGS 11

WEIGHTS AND MEASURES; SIGNS AND SYMBOLS . . 12

PHARMACY AND DISPENSING 14

MODES OF ADMINISTRATION OF DRUGS . . . 26

FACTORS MODIFYING DOSAGE 27

INCOMPATIBILITY 31

PRESCRIPTION-WRITING 32

TABLE OF APPROXIMATE EQUIVALENTS ADOPTED IN STATING DOSES, IMPERIAL AND METRIC, IN THE BRITISH PHARMACOPŒIA 1948 36

PART I.—THE INORGANIC MATERIA MEDICA . 37

GROUP I. THE METALS, AMMONIUM, METALLOIDS AND NON-METALLIC ELEMENTS 37

GROUP II. THE ACIDS 128

GROUP III. WATER, OXYGEN AND CARBON DIOXIDE . 133

PART II.—THE VEGETABLE AND ANIMAL MATERIA MEDICA AND SYNTHETIC PREPARATIONS 140

DRUGS MAINLY ACTING ON THE DIGESTIVE SYSTEM . . 140

I. COLOURING AGENTS 140

II. DEMULCENTS 141

III. FLAVOURING AGENTS AND CARMINATIVES—THE VOLATILE OIL SERIES 144
IV. SWEETENING AGENTS 155
V. BITTER STOMACHICS 158
VI. DIGESTIVES 162
VII. EMETICS 163
VIII. PURGATIVES 165
IX. CHOLAGOGUES 176
X. VEGETABLE ASTRINGENTS 177
XI. ANTHELMINTICS 181
XII. INTESTINAL ANTISEPTICS—ADSORPTIVE AGENTS . 186
XIII. INTESTINAL SEDATIVES 187
XIV. VITAMINS AND NUTRIENT MATERIALS . . . 187
DRUGS INFLUENCING METABOLISM—HORMONES . . 201
THYROID AND PARATHYROID HORMONES . . . 201
INSULIN 205
LIVER EXTRACTS 210
PITUITARY HORMONES 218
OVARIAN AND MALE HORMONES 220
DRUGS ACTING MAINLY ON THE HEART . . . 228
DRUGS ACTING MAINLY ON THE ARTERIES . . . 241
DRUGS INFLUENCING THE RESPIRATORY SYSTEM . . 254
DRUGS INFLUENCING THE NERVOUS SYSTEM . . . 260
CENTRAL NERVOUS STIMULANTS 260
GENERAL ANÆSTHETICS 268
ANODYNE NARCOTICS 290
ORGANIC HYPNOTICS 303
DRUGS ACTING ON GANGLIA 320
PERIPHERAL PARASYMPATHETIC STIMULANTS . . . 324
PERIPHERAL PARASYMPATHETIC DEPRESSANTS . . 332
LOCAL ANÆSTHETICS 341
ANTIPYRETICS 352

DIURETICS 369
URINARY ANTISEPTICS 372
DRUGS INFLUENCING GOUT 374
UTERINE STIMULANTS 377
EXTERNAL PROTECTIVES AND EMOLLIENTS . . . 384
ANTISEPTICS AND PARASITICIDES 394
COUNTER-IRRITANTS 432
DIAGNOSTIC DYES 440
VACCINE AND SERUM THERAPY 441

PART III.—PHARMACOLOGY AND GENERAL THERAPEUTICS 458
CHAPTER I. THE FOUNDATIONS OF RATIONAL TREATMENT 458
,, II. THE MOUTH 463
,, III. THE STOMACH 473
,, IV. THE DUODENUM AND INTESTINE . . 487
,, V. THE LIVER 504
,, VI. THE BLOOD 508
,, VII. METABOLISM 518
,, VIII. THE CIRCULATORY SYSTEM . . . 527
,, IX. THE RESPIRATORY SYSTEM . . . 540
,, X. THE NERVOUS SYSTEM 550
,, XI. THE KIDNEYS 562
,, XII. THE BODY-HEAT AND ITS REGULATION . 569
,, XIII. A. DRUGS ACTING ON THE SKIN . . 573
B. DRUGS ACTING ON THE EYE . . 576
C. DRUGS ACTING ON THE GENERATIVE SYSTEM 578

APPENDIX 579
I. DRESSINGS AND THEIR MEDICATION . . . 579
II. MASSAGE AND REMEDIAL EXERCISES . . . 580

III. BATHS AND ALLIED MEASURES 582
IV. MINERAL WATERS—SPAS 584
V. ELECTRO-THERAPEUTICS 587
VI. RADIUM AND RADIUM BROMIDE 590
VII. OUTLINES OF INVALID DIET 591
VIII. DANGEROUS DRUGS ACTS 595

INDEX xi

THE PHARMACOLOGY AND THERAPEUTICS OF THE MATERIA MEDICA

PHARMACOLOGY and Therapeutics define respectively the reasons and the indications, together with the methods, for using drugs and other remedial measures in the treatment of diseases. The place which these subjects should occupy in Medical Education rests logically between Anatomy, Physiology and Biochemistry on the one hand, and Medicine and Surgery on the other hand; while they should be learned concurrently with Pathology, the other stepping-stone from the more purely scientific to the practical and clinical aspects of the medical curriculum. The student will now be able to apply his knowledge of Physiology and Biochemistry, and to appreciate that these sciences are the foundations of scientific pharmacology and rational therapeutics; and, after reading the section on General Therapeutics, the reader will be in a position to appreciate properly the relative values of the drugs used in the treatment of disease.

Various sciences and arts, some of which are of little importance for students and practitioners of medicine, influence the selection of suitable materials for medical treatment; some of these will now be discussed.

Materia medica is a term applied to the materials or substances used in Medicine, their names, sources, physical characters and chemical properties, the preparations made from them, and the doses in which they may be given.

Pharmacognosy is the knowledge of the botanical features of medicinal plants, the microscopical characters of sections and powders of their useful portions.

Pharmaceutical Chemistry is concerned with the structure of their active principles, and the synthesis of these and other remedies.

Pharmacy is the name applied to the art of making the preparations required by the pharmacologist, and of dispensing the combinations prescribed by the therapeutist (*see* p. 16).

Pharmacology defines *the actions of drugs upon the healthy animal organism*, or the **physiological actions** of drugs.

Chemotherapy, a branch of Pharmacology, is concerned with the synthesis of chemical agents which have a high toxicity towards bacterial or protozoal organisms associated with a relatively low toxicity towards man or other infected host, e.g. sulphonamides, anti-malarial drugs.

Therapeutics is the science and art of treating diseases. It includes, therefore, the use of all means that contribute to the alleviation of symptoms and to the cure of the disease; that is, the employment not only of drugs but also of such remedial measures as sera, diet, nursing, clothing, baths, climate, and other means which may assist restoration of health, one of high importance, outside the scope of this book, being surgical treatment. Several of these measures will receive attention in this volume, but its main concern is with *medicinal therapeutics*, that is, the remedial uses of suitable inorganic and organic preparations.

In the first and second Parts of this work, the special pharmacology and therapeutics of each remedy and its preparations will be discussed; and the drugs are so arranged that those having similar pharmacological actions and therapeutical applications are grouped together.

An ideal therapeutical grouping of drugs cannot, however, be attained, since many of them have important actions on more than one organ or system. Hence in the concluding Part of this book—GENERAL THERAPEUTICS—the actions and uses of the remedial agents are correlated and compared in reference to the various systems—digestive, circulatory, etc.—so as to afford the student a survey of the influences which drugs and other therapeutic means exert on the physiology and pathology of the body.

THE BRITISH PHARMACOPŒIA

The number of drugs used within historical times has been enormous, and comparatively few of these have proved useful. In order to separate the valuable drugs from those of less importance there have been published from time to time, by the governments or medical authorities of different countries, books which furnish authoritative descriptions of the drugs generally recognized and used by the profession, and of the preparations made from them. These books are known as *pharmacopœias*, and the remedies they contain are spoken of as *official*. As a criterion in Great Britain, Northern Ireland, Eire, and the British Commonwealth of Nations, there is the **British Pharmacopœia 1948,** which affords a very accurate list of the drugs and preparations in use at the time of its publication. But, as pharmacology is a rapidly advancing science, especially from the directions of chemistry and physiology, and as opinion is often changing on the subject of therapeutics, the pharmacopœias of different countries vary greatly; in consequence, the pharmacopœia of any given country may not be regarded at the time of its publication as perfect, nor remain a correct representation of professional opinion for any great length of time. It is, however, a necessary provision for ensuring the purity and standard quality of medicines supplied to the public, and furnishes the physician and the pharmaceutical chemist with formulæ for a great variety of preparations of definite composition, and with information useful in selecting the drugs, in combining them, and in devising fresh preparations.

In order to keep the British Pharmacopœia abreast with recent advances in pharmacology and therapeutics, ADDENDA are published when required.

The British Pharmaceutical Codex 1949 and the Extra Pharmacopœia, issued under the authority of the Pharmaceutical Society, contain much valuable information regarding both official and non-official drugs employed as remedies, and about formulæ which have been found useful.

The National Formulary 1949 contains useful prescriptions for drugs in common use and gives substitutes for scarce and proprietary drugs. It should be adopted as a basis for prescribing.

PLAN OF THIS WORK

In the British Pharmacopœia the materia medica are arranged alphabetically. In this book, to facilitate the work of junior students, drugs which have comparable pharmacological actions are arranged together; and the actions of the various drugs influencing particular organs of the body are considered under General Therapeutics. Advanced students should read first the synopses of the Pharmacology of the system in Part III; then study the details of the individual drugs influencing that system in Parts I and II; and, finally, correlate this knowledge by further reference to Part III, particularly to the therapeutical section, which indicates the practical values of the drugs in disease.

PART I.—THE INORGANIC MATERIA MEDICA

The Pharmacology and Therapeutics of:—1, the Metals, Ammonium, Metalloids and Non-metallic Elements; 2, the Acids; 3, Water, Oxygen and Carbon Dioxide.

PART II.—THE ANIMAL, VEGETABLE AND SYNTHETIC MATERIA MEDICA

The Pharmacology and Therapeutics of Drugs acting on:—1. The Digestive System; 2. The Blood, and Metabolism; 3. The Circulatory System; 4. The Respiratory System; 5. The Nervous System; 6. Heat Regulation and Fever; 7. The Urinary System; 8. The Uterus; 9. The Skin, etc.; 10. Vaccine and Serum Therapy.

PART III.—APPLIED PHARMACOLOGY AND GENERAL THERAPEUTICS

PART IV.—APPENDIX

1. Dressings and their Medication; 2. Massage and Remedial Exercises; 3. Baths and Allied Measures; 4. Mineral Waters—Spas; 5. Electro-therapeutics; 6. Radium; 7. Outlines of Invalid Diet.

Each article of the materia medica in Parts I and II is discussed under several headings, as follows: The *names* of the drug in Latin and in English, its *chemical formula* or *composition*; the *definition of its nature*; its *source*; its *characters*; its *doses*; the *preparations* made from it; and its *actions and uses.*

General reference must now be made to these headings.

NAMES, NATURES AND SOURCES OF DRUGS

The *inorganic* materia medica includes some elements and a great variety of their chemical compounds.

Vegetable drugs are derived from entire plants, including fungi, stems (woods), roots and rhizomes, barks, leaves, buds, flowers, fruits, and seeds; and various vegetable products, including fixed and volatile oils, resins, oleo-resins, balsams, gums, gum-resins, dried juices, and secretions. The *animal* materia medica includes an entire insect, parts of animals, e.g. lard, and products, e.g. hormones, formed during life. *Synthetic* drugs are derived from various organic chemical compounds.

CHARACTERS OF DRUGS

The science of identifying crude drugs, *Pharmacognosy*, is now of little importance to the medical student, but an acquaintance with the chief physical and chemical properties of the drugs is a valuable aid to efficient and elegant prescribing. (1) A knowledge of the *physical characters* is best acquired by comparison of the description with actual specimens, when particular notice should be given to the character or absence of *smell* and *taste*. (2) The *pharmaceutical chemistry* of a drug includes its *reaction*; its *solubility* in water, alcohol, ether, oils, etc.; its behaviour to *heat*; and its *chemical interactions* with the body-fluids and other drugs. This information enables the prescriber to order the drug in a suitable form or solvent and to avoid chemical incompatibilities (*see* p. 31); and it also assists the student to understand the changes which drugs undergo in the tissues and the manner in which they are excreted.

The student should also know that there are simple *tests* for the more important and toxic drugs—not for forensic reasons—but because he may find tests useful in ascertaining whether the patient is taking and excreting the drug. In the case of inorganic drugs, these tests involve merely elementary chemical principles. The important tests for alkaloids, such as Morphine and Strychnine, and other organic compounds will be stated under each.

Impurities.—Impurities may occur in drugs owing to imperfect selection, preservation or preparation, or from chemical decomposition during storage.

The Pharmacopœia defines the limits of permissible impurities in different drugs and the tests by which they are detected and estimated. A knowledge of these is of small importance to the medical practitioner who relies upon the pharmacist to supply drugs conforming with pharmacopœial standards of purity and activity.

Composition of Drugs

The composition of inorganic drugs is expressed by their names and formulæ.

Vegetable drugs are frequently of highly complex composition, the chief active principles being the following: Fixed oils, volatile oils, resins, oleo-resins, gums, gum-resins, balsams, alkaloids, glycosides, neutral substances, acids, starch, sugar, pectin, cellulose, albuminous substances, enzymes, colouring matters, salts, and extractives.

A **Fixed Oil, Oleum,** is extracted by expression (if possible without the aid of heat) from the seeds or fruits of plants, or from animal tissues. Fixed oils are the esters of fatty acids (oleic $H,C_{18}H_{33}O_2$, palmitic $H,C_{16}H_{31}O_2$, and stearic $H,C_{18}H_{35}O_2$, as well as others less common) with the radical glyceryl C_3H_5. They are split in the intestine by lipase. With caustic alkalis or metallic oxides they form **soaps**; the metal combining with the acids and displacing the glyceryl, which is hydrated and becomes glycerin, $C_3H_5(OH)_3$.

$$\underset{\substack{\text{Sodium}\\\text{Hydrate.}}}{3NaOH} + \underset{\substack{\text{Glyceryl Oleate}\\\text{(Vegetable Oil).}}}{C_3H_5(C_{17}H_{33}COO)_3} = \underset{\substack{\text{Sodium Oleate}\\\text{(Hard Soap).}}}{3C_{17}H_{33}COONa} + \underset{\substack{\text{Glyceryl Hy-}\\\text{drate (Glycerin).}}}{C_3H_5(OH)_3}.$$

Volatile Oils; Resins; Oleo-resins; Balsams.—A volatile oil, **Oleum,** so-called essential or ethereal oil, is obtained mainly by distillation from entire plants, flowers, fruits or seeds. Most volatile oils are colourless when pure, and highly aromatic. They vary in composition. The majority contain liquid hydrocarbons, called **elæoptenes,** which are pinenes or terpenes $(C_5H_8)_n$, e.g. pinene, $C_{10}H_{16}$, in Oil of Turpentine. In addition, most contain oxidized aromatic hydrocarbons, termed **stearoptenes,** which chemically are alcohols, phenols, ketones, etc., and may be separated by cooling the oil or by fractional distillation. These are usually crystalline solids, e.g. Menthol, Thymol, and Camphor, rarely liquid, e.g Eucalyptol. Volatile oils are only sufficiently soluble in water to impart their odour and taste to it, but are freely soluble in alcohol, ether and chloroform.

Resins are solid and brittle substances, e.g. Colophonium, and Podophyllum resins. They are separated from **Oleo-resins** by distillation, are insoluble in water, soluble in alcohol, and form soaps with alkalis. Resins or Oleo-resins containing benzoic or cinnamic acids are called **Balsams,** e.g. Peru, Tolu. Oil of Cade and Pix Liquida are *empyreumatic oils*, produced by the destructive distillation of wood.

Gum, Gummi, is an exudation from the stems of plants. Gum Acacia consists of *arabin* which hydrolyses into glycuronic acid, arabinose and galactose. Tragacanth Gum contains a soluble gum yielding, on hydrolysis, geddic acid and sugars while the insoluble portion yields bassoric acid and sugars. Acacia forms a colloidal solution with water; Tragacanth is not wholly soluble but swells to form a colloidal "gel"; these products are called *mucilages*. **Pectin**, vegetable jelly, occurs in some medicinal plants and, like the mucilage in several others, is allied to gum. **Oleo-gum-resins,** e.g. Myrrh, Asafetida, are exudations from plants, containing various proportions of gums and resins, with volatile oil. When rubbed with water, gum-resins yield an *emulsion* in which the particles of undissolved resin are suspended by the mucilage in the form of a colloidal "sol."

Alkaloids are basic nitrogenous compounds, found in plants. They possess a pyridine (Nicotine, Coniine), pyrrolidine (Atropine, Cocaine), quinoline (Quinine), isoquinoline (Papaverine, Narcotine), or phenanthrene (Morphine, Codeine) nucleus, and, like alkalis, turn red litmus-paper blue and form salts with acids. As a rule they are crystalline solids, rarely liquids, e.g. Coniine, Nicotine, Lobeline, Pilocarpine; *they dissolve sparingly in water* but are readily soluble in alcohol; *their salts dissolve easily in water.*

Glycosides, e.g. Digitoxin, Ouabain, are ester-like combinations of sugars and are hydrolysed by acids of enzymes in presence of water into sugars and other compounds, *genins*, which differ in each instance, but are often phenols.

Saponins are nitrogen-free glycosides, solutions of which, by lowering surface-tension, froth on shaking, emulsify fats and resins, and cause hæmolysis of red blood-cells.

Neutral principles are active substances not conforming to any special group, e.g. Santonin, bitter principles.

Proteins.—Most drugs contain unimportant albuminous constituents, but the seeds of ricinus, croton and abrus yield highly poisonous *toxalbumoses*, ricin, crotin and abrin respectively, which are allied to the toxalbumoses of snake-venom and toxins of bacteria. Enzymes destroy these; they are highly toxic when injected, but, if injected in graded doses, the body becomes tolerant or immune to them.

Organic acids, e.g. malic, citric, oxalic, exist in plants combined with bases such as potassium, calcium and alkaloids, or free, e.g. tannic acid.

Doses

The Pharmacopœia suggests the range in the metric and imperial systems within which the different substances and their preparations may be given to an adult with advantage and safety (*see* p. 27).

Preparations of Drugs

The list of preparations made from the drug, with their principal ingredients, their strengths and their doses, will conclude the account of its pharmacy. These preparations require careful examination.

Most drugs possess such characters that it is necessary to prepare them for administration. Thus, if we take, as examples, Sulphur, one of the elements: Colocynthis, the dried pulp of a fruit: Cascara, a dry bark: and Coccus, a dried insect, it is manifest that these could not be brought into useful contact with the body in their natural states. Preparations must be made from them, and we must have a *variety of preparations* for several reasons. Firstly, drugs exist in various forms. Secondly, a substance may contain several active principles, soluble in different media, and it may or may not be desirable to extract together or separately. Thirdly, we frequently wish to obtain *combinations* of drugs, so as to increase, diminish, or otherwise modify the action of each, or to obtain combined actions. Fourthly, we must provide for variety in modes of administration or application, externally or internally; and we must also meet the wishes or convenience of patients by selecting pills, tablets, powders, etc., and obviating unpleasant tastes by giving the drug in cachets or capsules.

The following are the different kinds of preparations in the British Pharmacopœia.

Acetum, a *Vinegar*, is a solution of the active principles of a drug obtained by macerating it (*see* p. 15) in dilute acetic acid (not vinegar).

Aqua Aromatica, an *Aromatic Water*, is a very weak simple solution of a volatile substance in distilled water, obtained by (1) solution or solution with alcohol; (2) solution of a volatile oil, shaken and allowed to stand for 12 hours with 500 times its volume of Distilled Water; (3) by triturating the volatile oil with talc or kieselguhr and 500 times its volume of distilled water, and filtering; (4) by diluting a concentrated water.

Aqua Concentrata, a *Concentrated Water*, is a strong solution of a volatile substance in alcohol and water which, diluted with 39 times its volume of water, yields a product equivalent in strength to the corresponding Aqua.

Cataplasma, a *Poultice*, is a paste with a basis of Kaolin and Glycerin intended as a warming external application.

Collodium, a *Collodion*, is a solution of Pyroxylin and Resin in alcohol and ether, intended, on evaporation of the solvent, to leave a coating of Pyroxylin on the skin.

Cremor, a *Cream*—for external application—is prepared with a basis of Emulsifying Wax, Hard and Liquid Paraffin and Water.

Elixir, an *Elixir*, is a flavoured fluid preparation made by maceration and percolation.

Emulsio, an *Emulsion*, is a colloidal dispersion of two immiscible fluid drugs, an internal finely subdivided disperse phase in an external, usually aqueous, continuous phase. The stability is maintained by an emulgent, such as Acacia, Tragacanth, or Liquid Extract of Quillaia.

Extractum, an *Extract*, is an important kind of preparation and comprises a number of different classes, as follows:—

1. EXTRACTUM, the simple *Extract*, is prepared in various ways: (*a*) by macerating or digesting the drug with distilled water or alcohol; (*b*) by percolating the drug with chloroform water; or (*c*) by percolating the drug with ether (Extract of Male Fern); and finally evaporating these solutions to the required, usually a soft, consistence.

2. EXTRACTUM SICCUM, a *Dry Extract*, is prepared by percolation of the drug with distilled water or alcohol and evaporation to dryness.

3. EXTRACTUM LIQUIDUM, a *Liquid Extract*, is prepared by several different methods:—(*a*) Percolating the drug with distilled water, chloroform water or alcohol; (*b*) percolating the drug first with light petroleum to remove fat and then with alcohol (Colchicum), or with alcohol acidified with tartaric acid (Ergot); (*c*) macerating the drug in chloroform water, evaporating and adding alcohol (Senna); (*d*) dissolving in distilled water an extract prepared by precipitation with dehydrated alcohol (Liver).

4. EXTRACTUM COMPOSITUM, a *Compound Extract*, is prepared by macerating a drug in alcohol and evaporating, other drugs being then added.

The following extracts are standardized:—Belladonnæ Liquidum, Belladonnæ Siccum, Colchici Liquidum, Colchici Siccum, Ergotæ Liquidum, Filicis, Hepatis Liquidum, Hyoscyami Liquidum, Hyoscyami Siccum, Ipecacuanhæ Liquidum, Malti cum Oleo Morrhuae, Nucis Vomicæ Liquidum, Nucis Vomicæ Siccum, Stramonii Liquidum, Stramonii Siccum. A standard strength is attained (1) by testing the alkaloidal strength before the last step in the process; or (2) in Dry Extracts, by testing the alkaloidal strength of the crude drug and also the total solids and alkaloidal strength of the percolate, and thus estimating the amount of crude drug or diluent which it may be necessary to add in order to bring the alkaloidal strength to the correct percentage.

Gelatinum, a *Gelatin* or *Paste,* is a suspension of Zinc Oxide in Gelatin, Glycerin and Water.

Glycerinum, a *Glycerin,* is a solution of a drug in glycerin, with or without the aid of heat and water.

Infusum Recens, a *Fresh Infusion,* is prepared by steeping the drug in cold water for 15–30 minutes and straining, e.g. Calumba and Quassia. Fresh infusions should be used within twelve hours of their preparation.

Infusum Concentratum, a *Concentrated Infusion,* is made by macerating or percolating the drug with dilute alcohol or cold water. When diluted with seven times its volume of water, it forms a preparation, **Infusum,** equal in strength, but not in flavour, to a corresponding Fresh Infusion.

Injectio, an *Injection,* is a sterile preparation intended to be given by subcutaneous, intramuscular, or intravenous injection. They are either:—(*a*) sterile solutions of alkaloidal salts or other active drugs with a small dose in Water for Injection, or Injection of Sodium Chloride; (*b*) sterile solutions of drugs (e.g. Menapthone, Progesterone) in Ethyl Oleate or a suitable (Arachis) oil; (*c*) suspensions of insoluble Bismuth salts in Dextrose and Water for Injection, or in Arachis oil; (*d*) a dilution, prepared immediately before use of a sterile alcoholic solution with 9 times its volume of Injection of Sodium Chloride (e.g. Digoxin); or (*f*) oils or esters. Some injections contain Phenol or Chlorocresol as bacteriostatic agents; others Sodium Metabisulphite as an antioxidant, while the Sodium salts of barbiturates and sulphonamides are required to be prepared with Water for Injection free from carbon dioxide. Injections of drugs liable to decompose in air are made by dissolving the drug, obtained from a sealed container, in Water for Injection immediately before use, e.g. Neoarsphenamine.

Lamellæ, *Discs,* are discs of gelatin with some glycerin, containing a fractional quantity of a salt of an alkaloid. They are intended to be placed within the lower eyelid.

Linimentum, a *Liniment* or Embrocation, is a preparation suitable for application by rubbing, anointing or painting.

Liquor, a *Solution.* Liquors or Solutions consist of substances, other than volatile oils, dissolved in water or in alcohol, solution being assisted by various means.

Lotio, a *Lotion* or Wash, is a suspension of zinc salts for external application.

Mistura, a *Mixture,* is either a solution of various drugs or a dispersion of insoluble powders in water.

Mucilago, a *Mucilage,* is a solution of a gum.

Oculentum, an *Ointment for the Eye,* has a sterilised basis of wool fat and soft paraffin containing a mixture of substances, intended to act upon the eye.

Oxymel, an *Oxymel,* is a preparation containing purified honey and acetic acid and water, or these and an active principle.

Pasta, a *Paste,* is an unctuous preparation containing starch, for external use.

Pilula, a *Pill.* The Pharmacopœia gives the ingredients of pills, together with some suitable excipient by means of which these can be made into a uniform mass of soft consistence. The mass can then be divided into spherical pills of the required dose (*see* p. 20). Pills are usually complex. The substances best adapted for administration as pills are those that cannot for some reason be conveniently prescribed in fluid form, and that are intended to act locally in the bowel or to be absorbed slowly.

Pulvis, a *Powder*, consists of dry insoluble drugs reduced to powder and intimately mixed and sifted.

Spiritus, a *Spirit*. Spirits belong to three classes—(1) *Spiritus Methylatus Industrialis* (alcohol 95%). (2) *Simple Solutions in Rectified Spirit* (alcohol 90%) of volatile substances, including essential oils, in the latter case of the strength of 1 in 10. (3) Complex *Distillates*, prepared in a special manner.

Suppositoria, *Suppositories*, are conical solid bodies for introduction into the rectum, where they are intended to melt. They are composed of one or more active ingredients and oil of theobroma or gelatin with glycerin.

Syrupus, a *Syrup*, is a fluid preparation containing much sugar.

Tabellæ, *Tablets*, are solid discs made by compressing in granular form, or moulding, a drug or mixture of drugs commonly with the addition of an inert diluent and possibly with a disintegrating agent (e.g. starch). Tablets should dissolve or disintegrate in water at 37° C. in not more than 15 minutes. Two are made with a chocolate basis. Unless issued on a medical prescription, the pharmacopœial tablets must be labelled with the name of the tablets and the quantity of the active ingredient or ingredients in each tablet.

Tinctura, a *Tincture*, is a solution of active substances in alcohol, either alone or combined with other solvents. Tinctures may be grouped according to (1) the solvent, (2) the process, or (3) the ingredients employed. These are various:

1. SOLVENTS.—(*a*) *Alcohol* 45 to 90% is chiefly used. (*b*) *Tinctura Ammoniata*, the ammoniated tincture, is made with solution of ammonia in addition to alcohol.

2. PROCESSES.—Tinctures may be prepared by—(*a*) *Simple solution* or mixture. (*b*) *Maceration*: Place the solid material in the whole of the solvent (*menstruum*) in a closed vessel for seven days, frequently agitating; strain; press the residue (*marc*); mix the two liquids; and filter if necessary. (*c*) *Percolation*: Macerate the drug or drugs for four hours in part of the solvent; pack in a percolator; add solvent to saturate the drug and allow to macerate for twenty-four hours; percolate slowly till three-fourths of the desired volume is obtained; remove the residue (*marc*) from the percolator, press and mix the expressed liquid and the percolate; and add fresh solvent to make the prescribed volume of tincture. (*d*) *Some tinctures are standardized*: Belladonna, Colchicum, Digitalis, Hyoscyamus, Ipecacuanha, Nux Vomica, Opium, Camphorated Opium, Scilla, Stramonium, Strophanthus.

3. INGREDIENTS.—A Tincture may be either *simple*, **Tinctura:** or *compound*, **Tinctura Composita,** i.e. it contains more than one active substance.

Trochiscus, a *Lozenge*, is a dry tablet of one or more active ingredients (uniformly divided or previously dissolved) mixed with a basis prepared with Sucrose, Gum Acacia, and Tincture of Tolu.

Unguentum, an *Ointment*, is a mixture of active substances with lard, wool fat, wool alcohols, benzoinated lard, emulsifying wax, wax, olive oil, or hard, soft or liquid paraffin, variously combined. The ingredients are either thoroughly mixed or melted together.

The following preparations are also in common use, but are not provided in the British Pharmacopœia:—

Applicatio, an aqueous suspension of a skin remedy. *Aurula*, a solid cone of gelatin or cacao-butter, containing an active ingredient for introduction into the external ear. *Bougia*, a solid cylinder of gelatin or cacao-butter with which a drug is incorporated for introduction into the urethra or nose. *Cachet*, a lenticular capsule of rice paper, to enclose a nauseous or insoluble drug. *Capsula*, a receptacle commonly made of gelatin, to enclose a nauseous or insoluble drug, either solid or liquid. *Charta*, a Paper, cartridge paper coated with mustard in rubber solution, and used like a plaster. *Collunarium*, a nasal wash. *Collutorium*, a mouth-wash. *Collyrium*, an Eye-wash. *Enema*, an Injection or Clyster, a liquid for injection per rectum. *Gargarisma*, a Gargle. *Guttæ*, drops for instillation into the eye or ear. *Haustus*, a Draught. *Insufflatio*, a powder to be blown into the throat, ear, or nose. *Naristillæ*, nasal drops. *Nebula*, an atomized spray. *Linctus*, a thin confection to be swallowed slowly in small doses for treatment of the throat. *Pastillus*, a Pastille, a soft lozenge containing glycerin and gelatin as its basis, and containing usually an antiseptic for the mouth or throat. *Pessus*, a Pessary, a large form of the suppository, administered per vaginam. *Pigmentum*, a solution to be painted on a part. *Solvellæ*, solution tablets. *Vapor*, an Inhalation, administered as a vapour either *dry* (drugs volatile at room temperatures) or *moist* (drugs volatilized from hot water at about 160° F.). *Vitrellæ*, crushable glass capsules, covered with cotton wool and a silk bag, for volatile drugs to be inhaled.

ACTIONS AND USES OF DRUGS

The preceding subjects are epitomes of much information furnished by the Pharmacopœia. The student must next make himself acquainted with the actions and uses of each drug, that is, its pharmacology and therapeutics. In the present work these will be discussed as far as possible upon a uniform plan:

1. **Local actions.**—When a drug is applied to an exposed surface, it may produce some effect or "act upon it." This action may be either *external*—on the skin, or on exposed mucous surfaces, such as the conjunctiva, e.g. causing anæsthesia; or *internal*—on the alimentary canal, especially the stomach and intestines, e.g. resulting in vomiting or purgation. Some drugs have only a local action.

2. **Actions in or on the blood.**—The great majority of active remedies are absorbed into the blood plasma, much less frequently into the red or white corpuscles: that is, they exist *in* the blood, but have little or no action *on* it. A few remedies, in overdosage, do impair the functions of the blood (see p. 512).

3. **Specific actions.**—Through the circulation, drugs enter the tissues and organs, alter the physical, chemical or physiological state of one or more of them, and are then said to have a *specific* action upon these, e.g. anæsthetics on the brain.

4. **Remote local actions.**—Medicinal substances, having passed through the tissues, are finally removed from the body by the excreting organs, either in the form in which they were administered, or as the products of their decomposition by the tissues. The kidneys are the usual excretory organs for drugs: the lungs ("breath"), skin, mucous surfaces and glands of the mouth, stomach, intestines and bronchioles, as well as the liver and mammary gland, eliminate them to a lesser extent. While passing through the excreting organs, a drug may not only alter their secretions, but also exert on their tissues remote actions, which may result from its chemical alteration, e.g. Sulphathiazole.

WEIGHTS AND MEASURES; SIGNS AND SYMBOLS

The weights of the British Pharmacopœia are (1) those of the Metric system; (2) those of the Imperial system.

1. METRIC SYSTEM

Measures of Mass

1 microgram (γ)	= the thousandth part of 1 milligram	=	$0{\cdot}\overbrace{00000}^{5}1$	G
1 milligram (mg)	= the thousandth part of 1 gramme	=	0·001	,,
1 centigram (Cg)	= the hundredth ,, ,,	=	0·01	,,
1 decigram (Dg)	= the tenth ,, ,,	=	0·1	,,
1 gramme (G)	= weight of 1 millilitre of distilled water at 4° C.	=	1·0	,,
1 kilogram (Kg)	= one thousand grammes	=	1000·0	,,

The capital G is the best contraction for gramme, and obviates confusion with gr. for grain.

Measures of Capacity

1 microl	= the volume at 4° C. of	0·001	G of water.		
1 centimil (Cl)	= ,, ,,	0·01	,,		
1 decimil (Dl)	= ,, ,,	0·1	,,		
1 millilitre, mil (Ml), *or* cubic centimetres, c.c.	= ,, ,,	1	,,		
1 litre (Lit)	= ,, ,,	1000	,,	(1 Kg).	

2. IMPERIAL SYSTEM

Measures of mass.—These are the grain, *granum*; the ounce (avoird.) *uncia*; and the pound, *libra*; with their conventional symbols, gr., oz., and lb. respectively.

1 grain = *granum*, gr.j.
1 ounce = *uncia* = 437·5 grains
1 pound = *libra* = 16 ounces = 7,000 grains

It is very common, though not officially recognized, to employ, for the sake of convenience, a weight between a grain and an ounce called the drachm, *drachma*, ʒ, to signify 60 grains; *not*, let it be observed, the eighth part of an ounce, as in the fluid measure. A 20-grain weight called the scruple, *scrupulum*, ℈, was formerly in use, but is now mostly discarded. The Pharmacopœia recommends that the use of the ʒ and ℥ symbols should be discontinued, since ʒ is employed to express both 60 gr. and 1 fluid drachm, and ℥ to mean 480 gr., sometimes 437·5 gr., and also 1 fluid ounce. To a dispenser the symbol ℥ always implies 480 gr., and oz. 437·5 gr. of a solid. Errors are avoided by stating weights of solids in grains and volumes of liquids in minims or fluid ounces only.

Measures of capacity.—The measures of capacity of the British Pharmacopœia and their symbols are the minim, *minimum*, min., or ♏; the fluid drachm, *drachma fluida*, fl. dr., *f*ʒ, or simply ʒ; the fluid ounce, *uncia fluida*, fl. oz., *f*℥, or simple ℥; the pint, *octarius*, O; and the gallon, *congius*, C.

1 minim = min.j, ♏j.
60 minims = 1 fluid drachm, fl.dr.j, *f*ʒj, ʒj.
8 fluid drachms = 1 fluid ounce, fl. oz.j, *f*℥j, ℥j.
20 fluid ounces = 1 pint, Oj.
8 pints = 1 gallon, Cj.

RELATION OF VOLUME TO WEIGHT

1 minim	is the volume at	16·7° C. (62° F.) of	0·9114 grain		of	water.
1 fluid drachm	,,	,,	54·6875 grains		,,	,,
1 fluid ounce	,,	,,	437·5 ,,	(1 oz.)	,,	,,
1 pint	,,	,,	8750·0 ,,	(1·25 lb.)		,,
1 gallon	,,	,,	70000·0 ,,	(10 lb.)		,,
109·7 minims	,,	,,	100 grains		,,	,,

Percentage Solutions.—In the Imperial system there is no simple relationship between volume and weight. One minim is the volume of 0·9114 grain of water, therefore a fluid ounce (480 min.) weighs only 437·5 grains. This complicates the calculation of exact percentage solutions, for example:—

With fluids: 4·8 min. in 1 fl. oz. (capacity 480 mins.) = 1 per cent.
With solids: 4·37 gr. in 1 fl. oz. (weight 437·5 gr.) = 1 per cent.

The correct relationship, therefore, in order to prepare a 1-per-cent. solution is to dissolve 1 gr. of solid in 110 minims capacity of water, but, for most practical purposes, it is satisfactory to use **the approximation that 4½ gr. or min. per solid or fluid ounce represents a 1-per-cent. solution, while ½ gr. or min. per fluid or solid ounce is about a 0·1-per-cent. solution.**

RELATION OF THE IMPERIAL STANDARDS TO THE METRIC STANDARDS

Standards of Weight

2·2 pounds	=	1 kilogram (Kg)
1 pound	=	453·59 grammes nearly.
1 ounce	=	28·35 ,, ,,
1 grain	=	0·065 ,, ,,

Standards of Capacity

1 gallon	=	4545·963 c.c. nearly.
1 pint	=	568·245 ,, ,,
1 fluid ounce	=	28·412 ,, ,,
1 fluid drachm	=	3·551 ,, ,,
1 minim	=	0·059 ,, ,,

and conversely for mass and capacity:

1 gramme = 15·4 grains
1 mil or cubic centimetre = 16·9 minims nearly

In all Pharmacopœial preparations described in this Manual, where the *relative* (not actual) amounts of the ingredients are stated, the metric system is followed; otherwise, solids are measured by mass, liquids by capacity, in accordance with the Imperial system.

Domestic Measures.—A *teaspoonful* is a convenient but not quite accurate measure of 1 fluid drachm, or 4 mils; a *dessertspoonful*, of 2 fluid drachms, or 8 mils; a *tablespoonful*, of half a fluid ounce, or 15 mils; a *wineglassful*, of 1½ to 2 fluid ounces, or 45–60 mils; a *teacupful*, of 5 fluid ounces, or 150 mils; a *breakfastcupful*, of 8 fluid ounces, or 240 mils; a *tumblerful*, of 10 to 12 fluid ounces, or about 300 mils. Wherever accuracy is desired, a graduated measure glass must be used. Some drops being twice as large as others, it is dangerous to prescribe "drops" of powerful remedies, especially for children; minims should be prescribed instead (*see* p. 17).

PHARMACY AND DISPENSING

It has previously been pointed out how various are the sources and kinds of the drugs which are employed in therapy. Few of these drugs are found in nature in a condition fit for administration as medicines; they require to be subjected to processes of purification, concentration, etc. Such processes constitute the art of pharmacy. Broadly speaking, pharmacy is divisible into four branches: (1) *Chemical Pharmacy*—the art of preparing remedies of definite chemical composition, e.g. acids, salts, carbon compounds and alkaloids. (2) *Galenical Pharmacy*—the preparation of drugs, or of preparations of such, having no definite chemical composition, e.g. extracts and tinctures. Modern practice aims at the standardization of these preparations, so that they shall contain an exact quantity at least of the active ingredients. (3) *Compounding*—the art of combining drugs or their preparations as ordered in a medical prescription. (4) *Dispensing*—strictly speaking, the method of packing, labelling, and delivering the medicine to the patient; the term, however, is often used to include compounding.

Chemical pharmacy and, to a great extent, galenical pharmacy are now largely relegated to the manufacturing chemist; compounding and dispensing constitute the work of the retail chemist, but in outlying districts this work may devolve on the medical man, and a knowledge on his part of the principles involved is essential.

CHEMICAL PHARMACY

The main principles of the pharmaceutical processes employed in the purification of crude drugs are those of chemistry. In the case of **dry preparations** the following processes may be necessary:—

(*a*) *Desiccation*, or removal of moisture, is especially necessary in succulent plants, which would otherwise undergo fermentation.

(*b*) *Comminution* or *pulverization*, the powdering of drugs, must be employed if the drug is in large masses. For this purpose drug mills may be used, or the process of *trituration* (*triturare*—to pound) in a mortar employed for dry materials. Occasionally the drug requires to be mixed with a harder substance to facilitate the process of reduction (*mediate pulverization*). Frequently the degree of fineness is specified in the Pharmacopœia; thus a No. 20 powder is one which passes through a sieve containing twenty meshes to an inch. *Levigation* consists in powdering the drug by rubbing it down with a fluid in which it is soluble.

(*c*) *Fusion* is the melting of a drug by means of heat, and is used in the preparation of toughened caustic.

(*d*) *Granulation* is the formation of an intimate mechanical mixture of several salts in the form of granules by heating them at 90° C. with brisk agitation.

(*e*) *Sublimation* is the volatilization by means of heat and recondensation of a solid substance, e.g. Sulphur.

(*f*) *Elutriation* consists in diffusing an insoluble powder in water, allowing only the heavier part to settle, and decanting the fluid, which contains the finer particles; the process is repeated till the requisite degree of fineness is attained.

For the production of **wet preparations** we may use—

(*a*) *Solution*, dissolving a solid in a fluid menstruum.

(*b*) *Maceration*, a process involving the steeping or soaking of drugs in a cold menstruum.

(*c*) *Digestion*, maceration at a higher temperature.

(*d*) *Infusion*, the process of extracting the active principles of drugs by pouring boiling water over them and allowing digestion to proceed for a prescribed time.

(*e*) *Decoction*, the extraction of active principles from drugs by boiling with water for a prescribed time.

(*f*) *Evaporation*, the removal of volatile liquids in order to concentrate a fluid.

(*g*) *Distillation*, the conversion of a liquid into vapour and its recondensation in liquid form. It is used to separate volatile from non-volatile substances. *Fractional distillation* is a modification by adjusting the temperature in order to separate liquids with different boiling-points.

(*h*) *Filtration*, the removal of solid particles by passing fluids through a semi-permeable material, e.g. filter-paper, which will obstruct the solid particles. *Straining* through muslin is rough filtration.

(*i*) *Percolation* consists in passing the menstruum slowly through a bed of the powdered drug in order to dissolve in the fluid the soluble materials contained in the drug.

(*j*) *Decantation*, the separation of the clear supernatant fluid from a sediment collected at the bottom of the vessel.

(*k*) *Decoloration*, the removal of colour from substances by means of various bleaching or adsorbing agents.

(*l*) *Defatting*, removal of fats by percolation with solvent ether or light petroleum.

(*m*) *Sterilization.*—Solutions of drugs intended for injection must be sterilized and kept in sterile sealed containers. The Pharmacopœial methods are: (1) Glass vessels and containers are sterilized by heating at 150° C. for one hour or in an autoclave at 115° C. for 30 minutes; (2) Solutions or preparations in suitable sealed containers are sterilized by maintaining them at 115°–116° C. in an autoclave for 30 minutes; (3) Solutions or preparations, to which a bactericide, Chlorocresol 0·2 per cent. w/v or Phenylmercuric Nitrate 0·002 per cent. w/v, has been added prior to distribution in sealed containers, are sterilized by maintaining them at 98°–100° C. for 30 minutes; (4) Solutions may be filtered through a sterile bacteria-proof filter and with aseptic technique filled into sterilized containers (but must be *tested* for sterility); (5) Solutions or suspensions in oil or ethyl oleate are distributed into containers which are finally sealed, or temporarily closed, and sterilized by maintaining them at 150° C. for one hour (temporarily closed containers are then sealed); if the drug will not tolerate this temperature, the oil or ethyl oleate is sterilized in this way and the solution or suspension prepared by aseptic methods; (6) Parenteral Injections: Solutions or preparations for injection are dispensed in containers sealed to exclude bacteria. Heat-vulcanized rubber caps for multiple-dose containers are first boiled in several changes of water and then boiled for 30 minutes, and stored for 48 hours, in the same bacteriostatic agent used in preparing the injection.

If the dispenser cannot apply the official methods, he must obtain the prescriber's approval for the method to be used. The special directions for sterilizing solutions of individual drugs are given in the Pharmacopœia.

PRACTICAL PHARMACY

Accuracy in weighing and measurement is of first importance; cleanliness and care also are always necessary, particularly in the compounding of potent drugs. The prescription should be read carefully, and any overdose or incompatibility must be noted. If the error be serious, reference must be made to the prescriber for authority before the product is dispensed.

Students should endeavour to visit a wholesale chemist's factory and see the mechanical production of emulsions, pills, tablets, etc.

Weighing and measuring of drugs.—The dispenser has to deal usually with small quantities in compounding prescriptions. Solids are stated in grains or drachms, or in grammes, and the simple beam dispensing scales are sufficient for all ordinary purposes. If minute quantities of drugs are ordered, an accurate chemical balance must be used. The dispensing scales should be provided with glass scale pans, of which the right-hand one is removable. The weights, as a rule, are placed on the left-hand pan, the drug to be weighed on the right. After weighing each drug, the scale pan should be wiped perfectly clean. Sticky substances and soft extracts should not be weighed directly on the scale pan; a piece of smooth glazed paper should be folded in two and a circle cut out from it; this provides two paper discs of equal weight. The one is placed on the weights pan and the soft material is weighed on the other, from which it may be removed by means of a knife.

The measurement of fluids is carried out in graduated measure glasses, commonly of two sizes, one holding in the Metric system 60 mils and in the Imperial system 2 fluid ounces, for measuring larger quantities, and one holding 10 mils and 2 fluid drachms, which latter serves also as a minim measure. These glasses are provided with line graduations both back and front, and in measuring fluids these two lines, the fluid, and the eye should be on the same level, which will show that the glass is being held vertically. The dispenser should hold the glass at the level of the eye, its base behind being held between the first and second finger of the left hand while the thumb in front acts as a support; the thumb-nail may be used to mark the level to which the fluid must be added. The adoption of this method prevents the fingers from interfering with the passage of light through the glass, and at the same time leaves the little finger free to hold the stopper of the bottle. In narrow measure glasses, capillary attraction is apt to occur, and the correct level is intermediate between the highest and lowest levels of the fluid.

Drops are occasionally ordered, but the practice is one which should be abandoned, since drops vary enormously in bulk, according to the viscosity of the fluid, the shape of the mouth of the bottle, etc. If they are ordered, the dispenser should conform with the International Agreement and measure the drops from a tube which at 15° C. delivers 1 gramme of water in the form of 20 drops.

MIXTURES

These are fluid preparations composed wholly of liquid ingredients or partly of solid constituents which may be soluble or insoluble in the menstruum. In the latter case they require suspension or emulsification. The menstruum (solvent or vehicle) is either good potable water, distilled water, an aromatic water, or an infusion. Their bulk may vary within certain ranges, but usually it is determined by the standard capacity of bottles, which are made in sizes for the Metric system to contain 50, 100, 200 and 500 Mils, and for the Imperial system to hold 1, 2, 3, 4, 6, 8, 12, 16 and 20 fluid ounces. Very commonly a 200-Mil or 6-oz. mixture is prescribed.

Remedies prescribed in mixture form should not react chemically with one another unless the specific new compound be desired as a remedy. The taste, colour and appearance should be agreeable.

Where the constituents are fluids, or solids soluble in the aqueous menstruum, few difficulties should occur in compounding mixtures. It is often advisable to mix the ingredients in a certain rotation; this can be learnt only from experience, but certain general rules may be formulated. With fluid preparations, add the tinctures first, syrups, etc., second, and water last, except when a very toxic preparation is prescribed; this should always be the final addition lest it be added twice. Where the mixture is to contain a soluble powder, this, if very soluble, may be placed in the bottle direct; if less soluble, it is best triturated in a mortar before addition; and if it is prescribed in amount which will not be dissolved by the vehicle, the process of trituration must be prolonged till the material is in a very fine state of subdivision, water being added to help.

It may be well to describe here the processes of trituration. When the substance consists of large crystals, "pounding" in a mortar is employed to reduce it. The pestle is firmly grasped in the palm of the right hand and sharp vertical strokes are delivered on the surface of the crystals. When the larger lumps have been reduced, a rotatory motion, contrary to that of the hands of a watch, is conveyed to the pestle from the shoulder-joint, the wrist and elbow being rigid.

Suspension.—If insoluble salts are ordered in mixture form they require to be suspended in the watery menstruum so as to allow of equable division in dosage. This is attained by increasing the viscosity of the fluid by the addition of gum or syrup.

For the suspension of most insoluble powders—e.g. Calcium and Magnesium salts, Rhubarb, etc.—Mucilage, either of Acacia or Tragacanth, or Compound Tragacanth Powder, is used; for Bismuth salts, Tragacanth is better. Suspensions are not made by simple addition of the powder to the mucilage in a bottle; if this were done, clumping would result. The mucilage, or powdered gum to which a little water has been added, is placed in a mortar and the insoluble powder added to it gradually, a light stirring motion contrary to that of the hands of a watch being kept up with the pestle held loosely like a pen between the fingers. When the powder is evenly distributed through the mucilage, water may be added. Without the aid of trituration, mixtures may be prepared by adding the powder to the bottle containing some of the water, and shaking; mucilage is then added; and lastly the remainder of the water; the presence of water at first prevents the clumping which would occur. The amount of mucilage or gum necessary to suspend insoluble powders varies, since some are light and some heavy. For heavy powders 15 mils or 4 fluid drachms of mucilage are sufficient in a 200-Mil or 6-oz. mixture; for light powders about 4 Mils or 1 drachm in a 200-Mil or 6-oz. mixture.

Suspension of resinous bodies.—The oleo-gum-resin, Myrrh, contains sufficient gum to suspend the resin in its composition, and when powdered and rubbed up with water it forms a milky mixture called a natural emulsion.

If balsams, pure resins, or tinctures containing resins be prescribed with water, the addition of gum is necessary to bring about suspension. Mucilage of Acacia is that most commonly used; it should be freshly prepared from lump Acacia, and free from acidity. The mucilage is placed in a mortar and the resinous body added gradually with trituration, finally the water is added to the resin and gum. The amount of mucilage necessary to suspend resins varies, but as a general rule these bodies require twice their bulk of mucilage or equal quantities of gum. All of the following require suspending agents: Tinctura Benzoini Composita, Tinctura Myrrhæ, Tinctura Tolutana, Extractum Filicis.

Emulsification of Oils.—The emulsification of fixed and volatile oils implies the dispersion of the oil as microscopical globules (disperse phase) evenly through the water (continuous phase). In order to prevent the oil globules from reuniting they must be covered with a film of emulgent, such as gum, or protein, or the oil must be converted into a soap by means of an alkali.

Such "oil-in-water" emulsions are used chiefly for internal administration of oils and are nowadays made to a much higher degree of dispersion by hand- or power-operated emulsifying machines or homogenizers. The higher dispersion, however, increases the viscosity which may be corrected by using less of the emulgent. For external applications, "oil-in-water" emulsions are made with Emulsifying Wax in a 4% watery dispersion as emulgent, or Unguentum Emulsificans Aquosum may be used as a basis.

(i) *Emulsification by Alkalis.*—Alkalis form good emulsions, and their preparation is simple. In general, Liquor Potassii Hydroxidi is utilized, and, of this, half the amount of oil present is employed. The Liquor Potassii Hydroxidi is placed in the bottle and the oil added gradually with agitation, and then the water, shaking again after each addition; or the Liquor Potassii Hydroxidi may be diluted with the water, added gradually and shaken with the oil. This principle is used to prepare Liquor Cresolis Saponatus.

(ii) *Emulsification by Saponins and Borax.*—The Saponins, by lowering surface tension, possess the power of emulsifying oils; the emulsion is not so permanent as a gum emulsion; saponins are mainly used for the emulsification of tars. The emulsion is made in the same way as that by alkalis, Tincture of Senega or Quillaia equal to 15% of the bulk of the oil, or 10 minims for each fluid drachm of oil, being added. Borax is occasionally useful as an emulsifying agent, 4 grammes to 100 Mils or 20 grains to each fluid ounce, of oil being allowed. The Borax should be dissolved in the water, and oil added drop by drop with agitation.

(iii) *Gum Emulsions.*—For emulsifying oils, Mucilage of Acacia is very frequently employed in the proportion of three or four of Mucilage to eight parts of oil. The Mucilage, which serves to form the initial (or primary) emulsion, is placed in the mortar and, during light trituration, the oil is added gradually—drop by drop at first—till emulsification starts, and then in steadily increasing quantities. That emulsification is taking place is indicated by the Mucilage becoming turbid and thicker, and by the peculiar "clicking" sound which becomes audible during trituration. When all the oil has been primarily emulsified, water may be added gradually while stirring constantly. The "cracking" of emulsions, or separation of the oil from the water, may be due to: (*a*) too rapid addition of oil to Mucilage, so that insufficient time for emulsification is allowed, (*b*) too rapid dilution with water, especially when stirring is interrupted. Instead of Mucilage, Pulvis Acaciæ 1 part to 4 parts of oil, or Pulvis Tragacanthæ Compositus 1 part to 6 parts of oil, may be used. The powdered gum may be converted into a mucilage by the addition of a little water; or, which is easier, the oil may be thoroughly mixed with the gum, 2 parts of water should be added at once and then the remainder of the water gradually to this initial emulsion. When tinctures, spirits or acid preparations are to be added to emulsions, they should be diluted with water before addition, since alcohol and acids tend to cause separation of the oil. When volatile oils are prescribed with fixed oils they are mixed and emulsified together. Yolk of egg is frequently employed as an emulsifying agent for Oil of Turpentine, Extract of Male Fern, etc.; half a yolk is sufficient to emulsify 2 drachms. For machine-made oil emulsions, a decoction of Irish Moss or Carrageen from Chondrus crispus, a sea-weed, is often used.

"Water-in-oil" emulsions are mostly used for external application as ointments, creams or liniments. Wool Fat is used as emulgent in the Oculenta, and Wool Alcohols is the emulgent with paraffins in Unguentum Alcoholia Lanæ from which Unguentum Aquosum is prepared with Distilled Water. A mixture of Wool Alcohols, 5% in soft paraffin will emulsify 3 times its weight of water.

Liniments, Lotions, Eye-washes, and *Draughts* are dispensed according to the same rules as mixtures.

POWDERS

Administration in powder form is particularly suitable for insoluble salts and for substances which in mixture form would be incompatible. Powders have also the advantage that the dose is accurately weighed out and that they keep well. But the taste of the ingredients is difficult to mask unless they are given in cachets or folded in rice-paper, which can be swallowed with the contents; deliquescent substances cannot be prescribed in this form.

The ingredients ordered in a powder may exist in the form of large crystals or as roots, stems, leaves, etc. These must be powdered in a mortar or drug mill before weighing. The requisite amount of each ingredient for all the powders ordered is placed in a mortar and the materials thoroughly triturated till they are in a fine and uniform state of subdivision and intimate mixture; a spatula is used to scrape off the powder adhering to the pestle or mortar. The powder papers being placed in a row, the necessary dose for each powder is either weighed and transferred from the scale pan to the individual papers, or the powder is divided into heaps on each paper, and, by adding and subtracting from the various heaps, judgment by the eye of equality in bulk of the powders is formed. The former method should always be adopted when dealing with very toxic ingredients. Powders vary much in bulk according to the specific gravity of their ingredients: 1/3 to 1½ grammes or 5 to 20 grains is an average weight. When heavy drugs with a small dosage, e.g. Calomel, are ordered in powder form, they should be diluted with some innocuous powder such as Lactose. The size of paper should be selected according to the bulk of the powder. For average-sized powders, papers of 4 in. by 5½ in. are suitable; for smaller powders, 3 in. by 4 to 4½ in. The paper utilized for wrapping powders is thin, glazed on both surfaces and dead white in appearance.

Folding of powder paper.—The paper is placed on the bench with the long side parallel with the dispenser, and the powder placed in the centre of the paper. The near edge is folded upwards to within 1/4 in. of the upper margin: the fold at the base is smoothed down. The projecting 1/4 in. of the far edge is folded down smoothly. The far edge is again folded towards the dispenser, so that it comes just to or a little over the middle line of the new breadth of the paper. This operation completes the preliminary folding. The paper is now turned round so that one narrow end projects beyond the edge of the bench; closing this end between two fingers of the left hand, the paper is lifted vertically, and, after tapping down any powder in the upper portion of the paper, the spatula, held in the right hand, is placed horizontally behind the paper at the position which is one-quarter of the paper's length and, against the edge of the spatula, the paper is bent backwards or away from the dispenser. The paper is next turned upside down, and again, after tapping down any powder in the unfolded end, the spatula is used as before to fold the upper end of the paper backwards so that the two ends of the paper meet at the middle line. The folds should then be flattened out between the spatula and the bench, and the powder evenly distributed in the body of the paper. Brass gauges of definite size are often used for arranging the folds of papers. The finished powders are finally set out in a cardboard box or in an envelope of suitable size. Occasionally a teaspoonful dose, etc., of a powder is directed to be taken; in such cases the powder is dispensed in a wide-mouthed bottle.

PILLS

The substances which are suitable for administration as pills are solid mineral and vegetable substances given in small dosage, and the solid or semi-solid extracts. Occasionally small quantities of tinctures, oils, etc., enter into pills. The pilular form is particularly suitable when administration of remedies has to continue for long periods, or when we wish to diminish the rate of absorption of the remedy, or when we wish to conceal the taste of objectionable substances. Drugs made up in pilular form remain stable, and incompatibility does not readily arise in their preparation.

Pill excipients.—In order to form a retentive mass from solid materials an excipient is necessary; the excipient binds the particles of the active constituents of the pill together and prevents the pills from losing their shape. The following are the most useful: (i) *Syrup of Liquid Glucose*, a very useful excipient; it forms a sticky mass which readily assumes a pilular consistence, and the pills when formed harden somewhat, but do not tend to crack. Syrup and treacle are also employed. (ii) *Glycerin of Tragacanth*, a mixture of powdered Tragacanth, Glycerin, and Water, which forms a stiff gelatinous mass. (iii) *Confection of Roses* forms a very satisfactory excipient for heavy insoluble powders such as Calomel. (iv) *Mucilage of Acacia* is sometimes of use for vegetable powders; the pills which it forms are, however, apt to harden and crack.

The making of pills.—Usually several pills are ordered, and the amount of material necessary for the whole number of pills is calculated. The solid ingredients are weighed, then placed in a small mortar and thoroughly triturated with the pestle, which should be one with a small head. A small amount of the excipient which has been selected is placed on the end of the pestle and worked into the dry powder in the mortar. The mortar is meantime rotated by the left hand so as to bring all parts of the mass within the play of the pestle. Whenever the mass tends to stick to the side of the mortar it is freed again by the spatula: in this way thorough mixing of the ingredients results. When sufficient of the excipient has been added to convert the dry powder into a tough tenacious mass, and the mixture of the ingredients appears uniform, the mass is removed from the mortar by the spatula and worked between the fingers and thumb till it forms a plastic ball. If the mass be too soft the addition of a little powdered Tragacanth will harden it, or the amount of materials for another pill may be incorporated. It is then placed on a clean tile and rolled out by means of a rigid spatula into a sausage- or pipe-shaped roll of uniform diameter, care being taken that the ends are flat, not conical. Pill tiles are provided with a graduated scale, and the mass is rolled out till its length is that of the number of divisions which corresponds to the number of pills ordered. By means of the spatula—or, better, a sharp knife—the roll is cut opposite the divisions into the requisite number of portions. These little portions are roughly rounded by the fingers, and placed on the tile along with a little dusting powder consisting of Lycopodium, French Chalk, or Starch, and they are then rotated below the pill-finisher—a little boxwood tray with a margin not so deep as the height of the pills—until quite spherical. Should the pills be too small for the pill-finisher, they may be rounded finally by rotating them between the tile and the flat spatula. It should be noted that pills containing tannic acid, soluble mercury salts, or iron salts necessitate the use of a bone or wooden spatula.

Pills may also be made with the *pill machine*. This consists of a long board with slightly raised margins; at one end the board is flat or has a tile let into it, in the middle is a piece of brass with semicircular gutters or grooves arranged longitudinally, which fit into those of a second brass plate in the movable handle of the machine. At the other end is a little tray for receiving the pills. In practice the pill mass is placed on the flat board of the machine and rolled into a pipe with the back of the handle till the pipe corresponds in length to the number of divisions equivalent to the number of pills. It is then placed on the brass plate and divided by pressing over it the grooved brass plate in the handle. A few short backward and forward movements, using both hands, suffice to round the pills, and with a forward motion of the handle they fall into the tray. Such pills often show traces of the machine and require subsequent finishing.

Pill varnishing and coating.—Before being varnished or coated the pills should be allowed to harden somewhat. A simple coating may be obtained by rubbing the pills under the pill-finisher with French Chalk or sugar while they are still moist. A solution of gelatin or albumin may be employed, the pills, fixed on the ends of needles, being dipped in the solution for a moment and then set up to dry. Coating with varnish is performed in the same way.

For the production of *pearl coating* the pills are lightly touched with a little mucilage and then rotated on the pill-finisher with some French Chalk. When no more chalk adheres, they are transferred to the other side of the pill-finisher and polished by rubbing them beneath highly glazed paper. In this way the pills acquire a highly polished dead-white surface. By the addition of a little carmine to the French Chalk a pink coating may be produced. *Sugar coating* may be similarly achieved, but the pills, moistened with a little syrup, are rotated in a circular box containing a mixture of equal parts of sugar and starch. *Silver coating* is produced by moistening the pills with a little mucilage and dropping them on silver leaf, which is transferred to a hollow spherical box in which the pills are gently rotated. *Enteric Coatings*: *Gelatin-coated* pills hardened by immersion in about 6% Liquor Formaldehydi for fifteen minutes will, when dry, resist peptic digestion. *Keratin coating* may also be used where pills are intended to remain insoluble till they reach the small intestine. Keratin, after purification, is dissolved (10%) in equal parts of strong ammonia and alcohol (90%). The pills are moistened with the keratin solution and rolled till the solvent evaporates. This process requires repetition in order to produce satisfactory results. *Salol* or *stearic acid coating* by dipping the pills in melted salol or stearic acid is sometimes used.

TABLETS, CACHETS, PASTILLES AND GELATIN CAPSULES

Compressed Tablets.—Powders and pills have now been replaced largely by compressed tablets. The drugs suitable for administration in this form are many vegetable powders, certain metallic salts, organic compounds and alkaloidal salts. Compressed tablets for oral administration average about 5 grains in weight, while those used to prepare solutions for hypodermic injection average about a grain. Tablets are usually made by machine compression of a drug or drugs in granular form mixed with an inert diluent, e.g. a sugar, and damped with a moistening agent. Starch may be added as a disintegrating agent and Liquid Paraffin used as a lubricant to prevent adherence to the dies of the tablet-making machine. Tablet Triturates or Moulded Tablets are made by pressing the drug, mixed with its diluent and moistened with alcohol, into a mould. The chocolate basis used for Nitroglycerin and Phenolphthalein contains cocoa powder, Sucrose, and Lactose. The Pharmacopœial tablets must conform to a uniformity in average weight, a standard for weight of the contained drug and a disintegration test requiring solution or disintegration in water at 37° C. within 15 minutes. Tablets are a highly convenient and accurate means of giving remedies.

Compressed tablets of alkaloidal salts for hypodermic administration are of great convenience on account of their portability, freedom from decomposition, and rapid solubility. Commonly, the tablet is placed in the barrel of the syringe and then sufficient sterile water or saline drawn up to dissolve it for injection.

Cachets.—These consist of two plate-shaped or rimmed discs made of rice-paper and varying in diameter from 1/2 to 1 in. The medicament —a powder possessing an objectionable taste, for example—is filled into one half and, after moistening the rims of both, the covering disc is inverted over the containing disc and the rims sealed by pressure. Cachet moulds, having apertures in a metal plate which hold the discs, are useful when quantities are being made.

Pastilles.—These are prepared with a basis of varying proportions of Gelatin and Glycerin into which are usually incorporated antiseptics for medication of the mouth and fauces.

Capsules.—Capsules are made from a basis of Gelatin and Gum Acacia, with Glycerin added if they be desired softer. The basis is moulded into two cylindrical halves, one of which slides into the other, and the ends are dome-shaped. Capsules, (*enteric-coated*), hardened by immersion in 2% Formaldehyde (6% Liq. Formaldehydi) for 15 minutes, or dipped in a solution of cetostearyl alcohol and shellac in acetone, resist gastric digestion. They are occasionally useful for the administration of nauseous remedies.

SUPPOSITORIES, BOUGIES, PESSARIES

These are solid preparations shaped for introduction into the rectum, urethra and vagina respectively. They are prepared with a basis which melts slightly below the temperature of the human body. Such bases are Oil of Theobroma (M.P. 35° C.) and Glycerin of Gelatin—the Suppositoria Glycerini of the British Pharmacopœia.

The ordinary suppository and bougie moulds contain 1 gramme or 15 to 16 grains of Oil of Theobroma, while pessary moulds may contain 2, 4 or 8 grammes or 30, 60 or 120 grains. In preparing suppositories the amount of materials necessary for all the suppositories ordered, plus one or two more to allow for loss, is weighed out. The Oil of Theobroma is placed in the suppository bath or in a porcelain capsule over a hot water-bath till it is *just* melted. The solid ingredients are powdered in the mortar, which should have been warmed slightly, and to them a little of the Oil of Theobroma is added and the two intimately mixed with a stirring rod to form a paste. This paste is scraped out with the spatula and added gradually to the rest of the melted Oil of Theobroma in the capsule, stirring constantly to ensure uniform mixture. When all the material has been incorporated, stirring is kept up till the mixture shows signs of thickening. The suppository mould is now opened and each half carefully lubricated with a little Linimentum Saponis to prevent the Oil of Theobroma sticking to the metal. The mould is closed again and the material from the capsule poured into the cavities, care being taken to leave a surplus of material over the top of the cavity to allow for contraction of the oil in cooling. When preliminary surface-cooling has taken place, the mould may be placed on ice in order to increase the rapidity of solidification; but if the surface has not first congealed before this is done, umbilication or pitting will occur at the base of the suppository, which may be rectified by melting some of the excess material and pouring it into the little pits. When the suppository mould has quite cooled, the superfluous material over the cavities in the mould should be trimmed off with a sharp knife; the mould is then carefully unscrewed, and with the aid of a sharp penknife the suppositories are gently separated at their bases. Should they refuse to come free, a sharp knock of the mould on the bench is often sufficient to detach them; or, guarding the warm fingers by a piece of paper, pressure may be exerted at the bases. When the suppository is removed from the mould, ridges may be carefully removed by the penknife. If the material has been well mixed and not too hot, the finished suppository is of uniform colour; but if the material has collected at the point, the Oil of Theobroma has been poured while too hot.

Glycerin of Gelatin suppositories are frequently ordered with soft extracts. For this purpose the Suppositoria Glycerini basis of the Pharmacopœia is employed. This consists of Gelatin 14, Glycerin 70, and Water 100 parts. The suppository basis is melted, and the extract rubbed down on a warmed tile with a little of the melted basis till a homogeneous mixture is attained. This is then added to the remainder of the melted gelatin basis in the capsule. When partially cooled the mixture is poured into the mould as before, but in the case of gelatin suppositories the mould must first be lubricated with Almond Oil. The excess of a gelatin suppository may be removed by cutting with a warm knife. Occasionally soft extracts are ordered with Oil of Theobroma; in this case the process is the same, a little water or alcohol being added to the extract in order to rub it down before the addition of the melted Theobroma. Once made, suppositories obviously should not be handled except when necessary. They are sent out in small partitioned boxes.

OINTMENTS

Common ointment bases are Lard, Benzoinated Lard, Paraffinum Durum, Molle and Liquidum, Cera Alba and Flava, Cera Emulsificans, Adeps Lanæ, Adeps Lanæ Hydrosus, and Alcoholia Lanæ. Mixtures of certain of these bases constitute the following serviceable emollient ointments: Unguenta Alcoholium Lanæ, Aquosum, Emulsificans, Emulsificans Aquosum, Paraffini and Simplex, into which active ingredients are incorporated. Emulsifying wax serves to form "oil-in-water" emulsions whereas Wool Fat and Wool Alcohols form "water-in-oil" emulsions for creams. The readily absorbed bases are Hydrous Lanolin, Wool Alcohols, and Lard; Paraffins are absorbed least. Ointments which have as a basis soft material such as Lard, Soft Paraffin or Lanolin may be made by a simple process of mixing on the cold tile. Where an insoluble powder is ordered in ointment form, the powder, whether amorphous or crystalline, should be very finely pulverized; it is then mixed on the tile with a small portion of the basis, and gradual addition of the rest of the basis carried out. Ointments are rubbed down with a flexible steel spatula. This should be laid flat on the ointment, which is rubbed down and mixed with a side-to-side motion, a second spatula being used to clean the one employed for rubbing.

Ointments containing such higher-melting bodies as Waxes, Wool Alcohols and Hard Paraffin require to be melted in a porcelain capsule over a water-bath; the high-melting ingredients are pared small and added to the capsule. When these are completely melted, the lower-melting ingredients are added and the mixture stirred constantly while cooling. Insoluble powders may be dusted on while the mass is soft, and stirred in, or they may be incorporated on the tile. When the mixture has cooled to a thick consistence, it is placed on the tile and rubbed down with the spatula as described above. After the mass has been transferred to the tile, small hard lumps of Wax or Paraffin may appear in it, due to the mass having been transferred to the tile before it has cooled sufficiently. When large quantities of ointment are ordered, they may be prepared in the mortar.

Extracts and liquids are incorporated in ointment bases in the same way as solid powders; in the former case the previous addition of a little water or alcohol is often necessary in order to soften the extract. Ointments containing acid substances or preparations of mercury, as these substances corrode steel, must be rubbed down with a bone or wooden spatula.

PLASTERS

Plasters are solid preparations which are rendered adhesive by the heat of the body, but are now obsolescent and no longer official. Some of them, such as those of Colophony, Soap, and Lead, were merely supporting plasters; others, for example Belladonna, contained active ingredients intended for absorption. They consisted of a plastic basis of Colophony, Lead Oleate and Hard Soap. Cantharidin Plaster was made with Cera Flava and Adeps Lanæ. When plasters are prescribed their dimensions and shapes are usually given in inches.

PRESCRIBING

When the practitioner desires to employ drugs for the purposes of treatment, he turns to his knowledge of the actions and uses of the materia medica, selects his remedies, and proceeds to order one or more of them, according to a recognized form or formula, which is called a *prescription.* This is a practical test of one's acquaintance with an extensive subject. The beginner should know, therefore, what points are specially to be kept before him. Briefly, they are the following:—

1. Selection of the remedy.—The choice of the drug should be the rational deduction from an accurate knowledge of the disease which has to be remedied or relieved, and of the means at our command for alleviating or curing it. How this choice is to be made will be discussed under General Therapeutics in the third Part of the work.

2. Selection of the preparation.—The drug having been determined, the particular preparation of it will be selected in accordance with the considerations discussed under the heading of Preparations (p. 7). The Pharmacopœia affords abundant choice, according to the channel by which it is to be administered. This naturally leads to consideration of the methods of administering drugs.

MODES OF ADMINISTRATION OF DRUGS

The activity of a drug may vary greatly with the channel by which it is administered; and, as the various absorbing surfaces of the body have different degrees of vascularity as well as different powers of absorption, the rapidity of entrance of a drug into the circulation varies with the mode of administration.

(*a*) **By the unbroken skin or mucous membrane.**—Drugs may be applied (lotions, dusting powders) or rubbed in (liniments, ointments); painted on (pigments, etc.); used as a gargle, eye-wash, or lozenge, insufflated into a cavity, or introduced as a bougie or suppository. The effect is usually local only, but may be general, many drugs being absorbed by the skin or exposed mucous membranes.

(*b*) **By application to wounds or skin diseases,** as lotions, dusting powder, pastes, creams or ointments.

(*c*) **Hypodermic or subcutaneous administration.**—By subcutaneous injection of sterilized and non-irritant drugs; by **interstitial injection or infiltration** into the subcutaneous connective tissues; by **intramuscular injection** into the gluteal or other suitable muscles, employed for slightly irritant, insoluble or oily substances, because, as the muscles are very vascular, absorption is more rapid and risk of necrosis less and, as they have fewer sensory nerves, there is less pain; or by **intravenous injection,** now very frequently employed, with strictly aseptic precautions; **intraperitoneal injections** are occasionally given. The recent introduction of the comprehensive term, **parenteral injection,** which may mean any one of these, is unscientific and dangerous as it may be misinterpreted.

(*d*) **Intraspinal Injections by Lumbar puncture.**—Injection of drugs into the spinal subarachnoid space is occasionally employed. The needle should be introduced 1 cm. to the side of the third lumbar spine and pushed upwards towards the median line till it enters the subarachnoid space as is shown by the flow of subarachnoid fluid. From 3 to 5 c.c. of this are allowed to escape, and then the same amount of warm physiological saline containing the drug is injected. Intracisternal Injections are also employed.

(*e*) **Pulmonary inhalation.**—Amyl nitrite and the general anæsthetics are, when inhaled, absorbed rapidly and produce their characteristic effects upon the body. Certain other volatile substances may be inhaled into the finer bronchioles and perhaps the alveoli with a view to local treatment. These drugs may, if very volatile, be inhaled "dry" from a handkerchief or mask, while the less volatile are vaporized with moisture in inhalers containing hot water (about 160° F.). Sprays or nebulizers are also used to create a fine state of subdivision in fluids for purposes of inhalation.

(*f*) **Administration by the alimentary canal.**—(i) By the mouth into the *stomach*, in order to obtain either a local effect on the stomach, or to secure absorption of the drug after its passage through this organ. Only small amounts of volatile drugs, of iodides and bromides are absorbed by the gastric mucosa.

(ii) *Intestine.*—When drugs are required to act in the intestine they must be of such a character that they will not decompose in the stomach. If liable to be altered by it, they must be given in enteric-coated capsules or pills.

(iii) *Rectal* administration in the form of suppositories or enemata.—A nutrient enema should be of 60–150 Mils or 2–5 fluid oz. bulk; an evacuant enema from 300–600 Mils or 10–20 fluid oz. or more. Drugs may have to be given by the rectum instead of by the mouth on account of some physical obstacle, repugnance on the part of the patient or irritability of the stomach, or to spare the stomach in conditions of exhaustion. Again, the action desired may be a local one on the rectum, to relieve pain, remove worms, or soften retained fæces. When using potent drugs in the rectum it is necessary to bear in mind that the absorbed drug may escape the liver, the great poison filter of the body, by means of the anastomosis between the hæmorrhoidal plexus and the internal iliac veins.

(*g*) **Administration by the genito-urinary system** may be effected by injections into the bladder, by bougies or injections into the urethra, or by pessaries or injections into the vagina or uterus.

(*h*) The **eye** may be treated with drops (guttæ), lamellæ or ointments (oculenta).

(i) Drugs may be applied to the **ear** by means of insufflations, drops, lotions or "aurules" (p. 11).

DOSAGE

Having selected the remedy and the mode of its administration from a knowledge of its pharmacology and its preparations, we next determine the dose to be ordered. Drugs have a "minimal threshold dose" below which they have no demonstrable effect; the reaction to them then increases in direct proportion (usually by logarithmic progression) to the dose until a terminal point of "maximal response" is reached. The Pharmacopœia indicates the minimum as the smallest useful dose, and the maximum as the largest usually given without special reason or caution to adults. Most oral doses may be repeated three or four times in 24 hours; in some cases, the usual daily dose is quoted. Experience alone can teach the practitioner how far he may safely and wisely depart from these limits, to which he is by no means tied by law. Several **modifying circumstances** that are to be taken into account with respect to doses must here be carefully noted.

(*a*) Certain **external factors** exert a slight influence on the activity of drugs. Cold delays the action of drugs. In hot countries narcotics and purgatives possess somewhat greater potency. People living in high altitudes are more sensitive to the action of drugs that in any way interfere with the respiratory function of the blood.

(*b*) The **form** in which a drug is prescribed may modify dosage. Drugs given in mixture form are more rapidly absorbed than when given as pills. A large dose of Quinine Sulphate in powder has less efficacy than a small dose dissolved by acid in a mixture, since much of the former remains undissolved and unabsorbed. Preparations of Digitalis, Strophanthus, Squill, Ergot and Pituitrin are apt to vary in composition and to lose strength on keeping. Since their active principles cannot be standardized chemically, the activity of such drugs must be assayed by pharmacological experiments on animals to ensure that these preparations are in a fresh and active condition.

(*c*) **Conditions affecting the organism.**—Although animals of the same or different species show variations in their reactions to drugs, differences of the responses to drug actions requiring modification of dosage in man are uncommon in general practice except in the circumstances now to be considered.

(i) *Age.*—The smaller and lighter the individual, the smaller must be the dose; that is, the dosage is inversely proportional to the weight of the person. There are several methods of estimating the dosage for children: Young's formula: $\frac{\text{Age}}{\text{Age} + 12}$ gives too small dosage after the age of eight; Dilling has shown that the nearest approach to the weight curve is attained by adopting the formula $\frac{\text{Age}}{20}$, or $\frac{\text{Age} \times 5}{100}$, when calculating with metric weights. Clark recommends dividing the weight in pounds by 150, the average adult weight. While we thus diminish the dose generally, particular care must be taken in prescribing for children drugs that act on the nervous system, especially Opium, since this system is still undergoing development in the child, and is in a peculiarly sensitive condition. On the other hand, children are fairly tolerant of purgatives, Calomel, Strychnine, Atropine and Digitalis. In old age, too, with the exception of purgatives and stimulants, dosage should be diminished somewhat, because the metabolic rate is slower and the excretory functions less efficient. Drugs that increase blood-pressure may also have to be avoided in the elderly.

(ii) *Sex.*—The female as a rule is more sensitive to drugs—partly because usually smaller and less strongly built; partly because somewhat more sensitive to drugs acting on the nervous system: we therefore empirically give only 7/8 of the average dose for the male. During *menstruation*, strong purgatives should be avoided, as they are likely to cause congestion of the pelvic organs. During *pregnancy*, gentle laxatives should be used and drastic purgatives avoided; the latter cause pelvic congestion and straining which may lead to abortion. Similarly, medicines that act on the uterus and irritant diuretics must be avoided, as well as drugs that cause a considerable fall in blood-pressure, which might lead to asphyxia of the fœtus through defective circulation in the placenta. Further, certain drugs, such as Morphine, Hyoscine, Mercury, Arsenic, Iodides, and hypnotics, like Chloral, can pass from the mother to the unborn child and are best avoided.

During *lactation*, minute amounts of Iodides, Bromides, Salicylates and Quinine are excreted in the milk but these are insufficient to influence the child, therefore there is no reason to withhold these remedies from nursing mothers.

(iii) *Frequency of administration.*—When administering drugs over long periods it may be advisable to diminish the dose to about half of the normal amount. Some foreign Pharmacopœias recognize a daily maximal dose, and in the British Pharmacopœia maintenance doses for repeated administration are specified in the case of some drugs. Where remedies such as emetics, purgatives or narcotics are to be given once only, the maximal dosage may occasionally be exceeded.

(iv) *Times of administration.*—It cannot be too strongly impressed on the student that the directions for the patient as to the times at which medicine is to be taken should bear definite relation to the purpose for which it is being prescribed. The direction "three times a day" is often written without forethought. While each case must be treated on its merits, certain rules can be formulated. General "tonics," hæmatinics and irritant drugs, in mixture or in pilular form, are best given three times a day after food, so that the remedy may be absorbed more readily, and that irritant drugs may be mixed with the food and so diluted. Drugs that are intended to influence the stomach, such as bitters and astringents, or bismuth as a sedative, are given before meals; digestive adjuvants and antacids after meals. Purgatives should be administered with reference to the time they take to act. If their action is slow, e.g. anthracene purgatives, they are given at bed-time; if rapid, e.g. saline purgatives, in the morning. If they are to be repeated, the interval between the doses should be such that opportunity is allowed for the first dose to act, and the reservation should always be made "till purgation occurs" or "till the bowels open." Astringent drugs used in treating diarrhœa need not be continued after purgations have ceased. Drugs intended to act on the respiratory or circulatory system are given as a rule every four or six hours, because by the end of these periods the activity of the previous dose has usually abated; but drugs rapidly excreted, like Salicylates, may require to be given at two-hourly intervals in order to maintain an effective concentration in the body. Remedies for headache are given every half-hour to two hours as may be required. Narcotics and hypnotics are ordered at bed-time, when the body and mind are prepared for rest.

(v) *Drugs possessing several actions.*—Large doses of drugs often produce effects differing from those of small doses. Thus the salts of heavy metals induce constipation in small doses, but in toxic doses cause diarrhœa from gastro-intestinal irritation. Again, Ammonium Bicarbonate and Ipecacuanha in small doses are expectorant, in large doses emetic.

(vi) *Channels of absorption.*—Since drugs produce their actions much more rapidly when injected subcutaneously, a smaller dose is employed. Generally speaking, the hypodermic or intramuscular dose is about one-third of that by the mouth and the intravenous dose one-half of that again; while the dose per rectum may be four times larger than the oral dose.

(vii) *Body temperature.*—The temperature in man varies within such small limits that this factor seldom interferes with dosage. Still, it must be borne in mind that in hyperpyrexia, Digitalis may have no action on the heart, and yet, if the dose be pushed, toxic effects may follow when the temperature falls. Again, central antipyretics often fail where the temperature is abnormally high.

(viii) *Synergism or Potentiation.*—If two drugs having identical actions, e.g. general anæsthetics, are given together, the result is complementary and usually a summation of their potencies which would also be achieved by a proportionately increased dosage of either drug; conversely a subtractive effect results with antagonists. But when two drugs, which have different modes or sites of action although a similar pharmacological effect, are combined, the result is commonly greater than that of simple summation. This enhanced effect is called Synergism or Potentiation. In other words, the combination of two drugs which produce the same type of action but by different methods will produce a more certain, speedy and considerable effect than a large dose of either of them. For example, Epsom Salt acts as a purgative by promoting the fluidity of the intestinal contents, whilst Senna stimulates the colon; and the two (combined in Mistura Sennæ Co.) form an efficient means of emptying the bowel. The alkaloidal narcotics, Morphine and Hyoscine, and the Barbiturates enhance considerably the effects of Chloroform and Ether and thus serve to reduce the amounts of these required to maintain general anæsthesia. Other examples are: Morphine and Chloral or Hyoscine as narcotics, Bismuth and Arsenic in syphilis, Ipecacuanha and Iodides as expectorants, Caffeine and Potassium Citrate as diuretics. Ephedrine and Amphetamine potentiate the action of Adrenaline, as does also Cocaine.

(ix) *Idiosyncrasy.*—In a restricted sense, this implies an abnormal reaction by a person to a drug; for example, in some people, Morphine causes an abnormal stage of excitement, preventing rather than promoting sleep, and small doses of Acetyl-Salicylic Acid or Phenazone sometimes cause erythematous rashes. In a wider sense, idiosyncrasy includes the *susceptibility* which some individuals show towards some of the toxic actions of certain drugs, e.g. Morphine, Mercury, Quinine, Iodides, Bromides, and Antipyretics, especially Amidopyrin. When using these drugs it is advisable to commence with a small dose until the patient's reaction to them is ascertained. Idiosyncrasy or susceptibility to a particular drug may arise from subsequent doses taken at some interval after an initial "sensitizing" dose has been given to the patient; this is comparable with the allergic or histamine-like reactions occurring from serum therapy. Such allergic types of reactions may occur from antipyretics, Thiouracil, Penicillin, etc., and are referred to under each drug.

(x) *Tolerance and drug habits.*—Tolerance may be natural or acquired. *Natural* tolerance is that possessed by certain animals towards some drug; it is rarely seen in individuals. *Acquired* tolerance of a drug is a result of frequent use of it. The classical example of acquired tolerance was the large doses of Arsenic taken by Styrian mountain races; this is explained, however, largely by the fact that the Arsenic is taken solid and no water with it, so that its absorption is reduced. The acquired tolerance for Morphine and Alcohol is explained by the increased powers of the tissues to oxidize these drugs. When a patient becomes dependent on a drug, craves for it and indulges in it to a vicious extent, he is said to have developed a *habit* for the drug, such as that for Cocaine, Morphine, Diamorphine, Chloral, Barbitone or Alcohol. Use of enemata may develop into a habit. Both tolerance and habit may necessitate increased dosage for remedial purposes.

(xi) *Cumulation.*—When a drug is given in such large doses or with such frequency that its excretion is incomplete or its action has not subsided, the action of the drug will accumulate. Thus drugs, such as Lead, Mercury, Arsenic, Sulphonal, Strychnine, Thyroideum and Digitalis, given with benefit at first, may in time commence to act as poisons owing to their cumulation.

(xii) *Disease.*—In diseased conditions the actions and the tolerance of drugs are frequently modified. Cocaine rarely causes an effective anæsthesia in inflamed tissues. Large doses of Quinine can be borne with ease and benefit in malaria; an antipyretic which powerfully reduces febrile temperature will not lower that of a healthy individual;

and Bromides lessen convulsion in epilepsy but have comparatively little action on a healthy man. Diarrhœa may delay absorption and fever minimize the effects of drugs. In diseases of the kidneys, when urinary excretion is defective, drugs eliminated by this channel, such as Strychnine, Digitalis or Arsenic, are retained in the system for a longer time and symptoms of poisoning may readily supervene.

INCOMPATIBILITY

A full appreciation of the subject of incompatibility can best be acquired by experience in compounding prescriptions and by a thorough knowledge of chemistry. Many drugs which are incompatible in a less degree can be combined with impunity, since the chemist can frequently compound the prescription in such a way that the incompatibility is either avoided or corrected.

Incompatibility may be physical, chemical or pharmacological. *Physical incompatibility* implies the difficulty, on account of their physical properties, of compounding without modification two substances together, e.g. fixed oils, volatile oils, resins and solutions containing them or insoluble powders with water. Again, the alcohol present in tinctures may throw water-soluble salts out of solution. *Pharmacological incompatibility* implies the combination in a single mixture of two drugs having opposite pharmacological actions, as would be a combination of Atropine with Pilocarpine, or Strychnine with Bromides. It is, however, occasionally advantageous to combine drugs which are pharmacologically incompatible. Thus Neostigmine, which improves the muscular impairment in myasthenia gravis by retarding the hydrolysis of acetylcholine at the myoneural junction, may have its undesired parasympathetic effects annulled by Atropine; and the griping tendencies of some purgatives can be obviated by volatile oils or Atropine. Drugs used like these to counteract untoward and undesirable actions of the more potent drug are termed *correctives.*

Chemical incompatibility implies the decomposition of one drug by another, but the term is usually restricted to instances where the result of the combination is an unexpected, inelegant, useless or dangerous compound. Thus, Ferric salts with drugs containing Tannic Acid yield an ink. Occasionally, however, it is advantageous to combine drugs which are chemically incompatible, e.g. in Pilula Ferri Carbonatis, and Mistura Magnesii Hydroxidi. Chemical incompatibility, as a hindrance to prescribing, is much overrated by students. The majority of incompatibilities are but slight, so that the dispenser can avoid or mask them, and the necessity to prescribe together drugs which are grossly incompatible rarely arises. We shall, therefore, state here merely the chief reasons for incompatibilities so that these may be generally avoided, and indicate, under the individual drugs, any special incompatibilities possessed by them.

(1) Two soluble salts may produce a precipitate, e.g. Lead Acetate with Sulphates, Silver Nitrate with Chlorides.

(2) Two soluble salts may form a new soluble double salt, e.g. Mercuric Chloride with Potassium Iodide.

(3) Acid or acid preparations will combine with hydrates, carbonates, bicarbonates and oxides of heavy metals to form salts, and a stronger acid will displace a weaker in a salt, e.g. Dilute Hydrochloric

Acid will decompose Liquor Ammonii Acetatis. Acids also decompose glycosides. Most instances will be avoided from chemical knowledge, but the student must note that some pharmacopœial preparations are acid although their names do not indicate this property. Those possessing this **"hidden acidity"** are:— Extractum Ergotæ Liquidum, Liquor Adrenalinæ Hydrochloridi, Liquors or Syrups of Iron or Mercury, Liquor Morphinæ Hydrochloridi, Preparations of Squill except the Tincture, Syrupus Limonis, Tinctura Ipecacuanhæ, Tinctura Opii Camphorata and Tinctura Catechu. Spiritus Ætheris Nitrosi is slightly acid if kept long.

(4) Alkalis or alkaline salts, e.g. carbonates, bicarbonates and hydroxides, will precipitate the soluble salts of the heavy metals and also alkaloids from their soluble salts. In this connection there have to be borne in mind some **"hidden alkalinities"** amongst pharmacopœial preparations:—Extractum Senegæ Liquidum, Infusum Senegæ Concentratum, Liquor Ammonii Acetatis Fortis and Dilutus, Liquor Arsenicalis, Liquor Cresolis Saponatus, Liquor Plumbi Subacetatis Fortis, Spiritus Ammoniæ Aromaticus, and Tinctura Valerianæ Ammoniata.

(5) Tinctures containing active principles insoluble in water may yield a precipitate in a watery mixture, e.g. Tincturæ Benzoini Composita, Myrrhæ, Opii Camphorata, and Tolutana.

(6) Tannic Acid, and drugs containing it, will form precipitates with alkaloidal salts, heavy metallic salts, and proteins.

(7) Bromides and Iodides usually produce precipitates with alkaloidal salts.

(8) Oxidizing agents will combine readily with oxidizable or reducing substances, and the Permanganate or Chlorate of Potassium and Chromii Trioxidum are best prescribed alone or not with organic drugs.

PRESCRIPTION-WRITING

In the new Pharmacopœia much greater prominence has been given to the metric system in stating the dosage of drugs. This tends to bring the subject of Pharmacology and Therapeutics into closer relationship with the more scientific branches of Medicine. From the ease with which percentage solutions may be prescribed, its greater simplicity in actual use, and the fact that it is almost universally employed by other countries, it should be accepted as the rational method by prescribers in this country. Mental arithmetic serves to convert grains or minims into grammes or Mils, and the tables of approximate equivalents, as recommended by the Pharmacopœia, are sufficiently accurate for practical purposes (*see* p. 36). It is customary in most countries where the metric system is in vogue to express the dose of liquids by weight also, and the figures in such prescriptions therefore refer to grammes. The difficulty introduced by this factor is that the specific gravity of liquids varies considerably. It is, therefore, advisable to adopt the plan of the Pharmacopœia, that solids be measured by weight and liquids by bulk. This causes no difficulty in compounding, since the dispenser can interpret the figures as grammes or Mils according as the drug ordered is solid or liquid respectively.

One apparent difficulty attached to the metric system is the disparity between the ordinary domestic measures and the metric measures. Under the imperial system a 6-fluid-ounce mixture with a tablespoonful

(1/2 oz.) dose gives twelve doses; whereas in the metric system, if we make up the mixture to 200 Mils (the nearest round figure corresponding with a bulk of 6 oz.), then a tablespoonful (15 Mils) gives thirteen doses and 5 Mils over. In practice, however, domestic measures are themselves so very variable in capacity that such an error is as likely to occur in the imperial system from the use of too small a tablespoon.

In the examples of prescriptions which will be given here both metric and imperial measures will be used, so that the student may study both methods. He is advised, however, to adopt the metric system.

COMBINATION OF REMEDIES IN A PRESCRIPTION

We combine drugs in prescriptions for several reasons, which may be stated shortly as follows:—

1. **To aid the action of the basis or principal ingredient.**—This may be attained.—(*a*) *By combining different preparations of the same drug.* Thus, for example, as gastro-intestinal sedatives we may combine Bismuth Carbonate and Salicylate. (*b*) *By combining the basis with substances which have a similar action.* This introduces us again to the use of *synergists*—drugs that, while acting by different methods, procure the same ultimate results. Thus, as a hypnotic we may combine Chloral Hydrate and Potassium Bromide; in cardiac disease, Digitalis and Squill; in hyperacidity, Magnesium Carbonate with Atropine; as an expectorant, Ammonium Bicarbonate or Ipecacuanha with Potassium Iodide; as a diuretic, Digitalis with Potassium Acetate, Caffeine or Calomel; and Opium improves the action of Ipecacuanha as a diaphoretic.

2. **To correct the operation of the basis.**—When drugs are irritant to the mouth and stomach, we may minimize this by prescribing them with demulcents, such as Glycerin or mucilage. Undesirable pharmacological actions may require "correctives," thus volatile oils as carminatives or Atropine preparations diminish the colicky pains produced by strong purgatives. Iron preparations tend to cause constipation, and to prevent this they are prescribed with Aloes or Cascara. Sodium Salicylate tends to irritate the stomach, but its decomposition to Salicylic Acid in the stomach is avoidable by giving with it Sodium Bicarbonate.

3. **To obtain a new active compound by chemical combination.**—Examples are the union of Ferrous Sulphate and Potassium or Sodium Carbonate to form fresh Ferrous Carbonate; and the combination of Mercuric Perchloride and Potassium Iodide to form Biniodide of Mercury.

4. **To procure a convenient and agreeable form by**—(*a*) prescribing pills, mixtures, tablets, etc.; (*b*) the exhibition of flavouring agents; (*c*) the suspension of insoluble powders by mucilage; and (*d*) colouring the mixture or coating the pill.

THE PRESCRIPTION

We are now in a position to analyse a prescription. It consists of four parts: the *superscription*, composed of a single sign, ℞, an abbreviation for *Recipe*, "take"; the *inscription* or body of the prescription, containing the names and quantities of the drugs ordered; the *subscription*, or directions to the dispenser; the *signature*, or directions to the patient, following *Signa*; and, lastly, the patient's name, the date, and the practitioner's name or initials. In what may be called a classical prescription, it was customary to arrange the constituents of the inscription under four heads, viz. the *basis*, or active drug proper; the *adjuvant*, or substance intended to assist, and especially to hasten, the action of the basis; the *corrective*, to limit or otherwise modify the action; and the *vehicle* or *excipient*, to bring the whole into a convenient, pleasant form for administration. To take an example:

Patient's Name and Address..

Superscription:		Recipe		
Inscription:	Basis	Magnesii Sulphatis	unciam cum semisse	50·0
	Adjuvant	Extracti Sennæ Liquidi	drachmas duas	8·0
	Corrective	Syrupi Zingiberis	unciam	30·0
	Vehicle	Aquam Menthæ Piperitæ	ad uncias sex	200·0
Subscription		Fiat Mistura		Misce
Signature		Signa (Signatur): One tablespoonful (15 Mils) in a tumblerful of water every morning before breakfast.		

Practitioner's Name or Initials ....

Date..........................

To analyse this prescription: The Magnesium Sulphate prevents the absorption of fluid from the bowel; the Liquid Extract of Senna stimulates colonic peristalsis and so helps the action of the basis; the Syrup of Ginger as a carminative corrects any tendency to griping, and the Peppermint Water serves as a flavour and solvent for the active constituents.

In the above example the quantities of the ingredients are calculated for the whole amount contained in the mixture. This entails calculation on the part of the prescriber; and many practitioners find it more convenient to prescribe the *single dose* of the drug, and to state the number of such doses to be sent by the pharmacist. The method has the advantage of showing at glance the actual dose of each ingredient:

Patient's Name and Address..

Superscription:		Recipe		
Inscription:	Basis	Tincturæ Ipecacuanhæ	minima decem	Dl 6
	Adjuvant	Tincturæ Scillæ	minima quinque	Dl 3
	Corrective	Syrupi Tolutani	semi drachmam	Ml 2
	Vehicle	Aquam Chloroformi	ad semi unciam	Ml 15
Subscription		Misce. Fiat Mistura. Mitte doses tales duodecim.		
Signature		Signa (Signatur): One tablespoonful in a wineglassful of water every four hours.		

Practitioner's Name or Initials..........................

Date..........................

It will be seen that the first three parts of the prescription are in Latin, the signature or directions in English, although these also may be written in Latin. The names of the drugs and preparations, except the vehicle when the quantity is indicated complementally, as in the prescriptions, are written in the genitive case, the quantities in the accusative governed by *Recipe,* as in the first prescription:

Recipe	Syrupi Zingiberis	unciam
Take	of Syrup of Ginger	one ounce

In practice the employment of extended Latin in prescription-writing has fallen into disuse, and we adopt contractions both for the names of the drugs and for the quantities ordered. It is seldom now that the directions to the patient are requested to be written in Latin, and there is no reason for the continuance of the practice. A few abbreviations and signs are allowed, viz.—℞ for *Recipe*; M., *Misce*; S. or Sig., *Signa*; āā, *ana*, of each; Ft., *fiat*, make; q.s. *quantum sufficiat*, a sufficiency; *ad*, up to, to amount to (the full phrase being *quantum sufficiat usque ad*); c̄., *cum*, with; no., *numero*, in number; p.r.n., *pro re nata*, as required, occasionally; t.d.s., *ter in die sumendus*, to be taken three times a day; b.d., *bis in die*, twice a day; a.c., *ante cibum* or *cibos*, before food; p.c., *post cibum*, after food; m.d.u., *more dictu utendus*, to be used as directed; rep., *repetatur*, let it be repeated; ss. *fs.*, *semi-* or (*cum*) *semisse*, a half.

The names of drugs must always be written in full whenever there can be the smallest possibility of error. It is not only inelegant but dangerous to use such abbreviations as Acid. Hydroc. Dil. and Hyd. Chlor. The Pharmacopœia gives suitable contractions which should be adopted.

The following are examples of prescriptions in abbreviated form for a powder, pill, suppository and subcutaneous injection: the Pharmacopœia, however, recommends the use of Arabic numerals:—

℞
Bism. Carb. } āā gr. v.
Sod. Bicarb. }
Pulv. Cret. Aromat. c̄. Opio, gr. x.
M. Ft. Pulv. Mitte tales sex.
Sig. 1 t.d.s., a.c.

℞
Cocain. Hydrochlor. gr. iii.
Ol. Theobrom. gr. xc.
M. Div. in supp. vi.
Sig. 1 inserted into the rectum every evening.

℞
Ext. Casc. Sag. Sicc. gr. xx
Ext. Nuc. Vom. Sicc. gr. ij
Syr. Glucos. Liq. q.s. ut fiat massa et div. in pil. vi.
Sig. 1 at night, if required.

℞
Inj. Insulin (20 Un. per Mil) min. CL (10 Mils)
Sig. 8 min. (0·5 Mil) to be injected hypodermically as directed ½ hr. before the morning and evening meal.

Prescriptions in the metric system.—Prescriptions in the metric system are written in exactly the same method as in the imperial system. As the British Pharmacopœia has adopted the principle of measuring solids by weight and liquids by capacity, the quantities, when specified by numerals only, can easily be interpreted by the dispenser. In practice the decimal point is used to separate quantities above unity from those below. but when stating a quantity below unity it is advisable to place a cipher before the point so as to prevent any misapprehension. Other prescribers adopt a straight vertical line, and place the figures above unity to the left and those below to the right of it. A third method consists in stating the metric doses in decigrams, decimils, etc., and prefixing the contractions for these measures, as is shown in the second prescription (p. 34).

TABLE OF APPROXIMATE EQUIVALENTS ADOPTED IN STATING DOSES, IMPERIAL AND METRIC, IN THE BRITISH PHARMACOPŒIA 1948

Gramme		Grain	Gramme		Grain
0·00012	..	1/500	0·0012	..	1/50
0·00015	..	1/400	0·0015	..	1/40
0·0002	..	1/320	0·002	..	1/30
0·00025	..	1/240	0·0025	..	1/24
0·0003	..	1/200	0·003	..	1/20
0·0004	..	1/160	0·004	..	1/16
0·0005	..	1/120	0·005	..	1/12
0·0006	..	1/100	0·006	..	1/10
0·0008	..	1/80	0·008	..	1/8
0·001	..	1/60	0·01	..	1/6

Mils or Grammes		Minims or Grains	Mils or Grammes		Minims or Grains
0·012	..	1/5	0·4	..	6
0·016	..	1/4	0·5	..	8
0·02	..	1/3	0·6	..	10
0·025	..	2/5	0·8	..	12
0·03	..	1/2	1	..	15
0·04	..	3/5	1·3	..	20
0·05	..	3/4	1·6	..	25
0·06	..	1	2	..	30
0·08	..	1⅓	2·6	..	40
0·1	..	1½	3	..	45
0·12	..	2	4	..	60
0·15	..	2½	5	..	75
0·2	..	3	6	..	90
0·25	..	4	8	..	120
0·3	..	5	10	..	150

If the following approximate equivalents are memorized, conversion of other equivalents becomes simple:—

1 gr. (min)	..	0·06 G (Mil)	1 mg.	..	1/60 gr.
60 gr. (min)	..	4 G (Mils)	0·1 G (Mil)	..	1½ gr.
1 oz.	..	28 G (Mils)	1 G (Mil)	..	15 gr.
1 lb.	..	0·45 Kg.	1 Kg.	..	2⅕ lb.
1 pint	..	0·56 Litre	1 Litre	..	1¾ pints

PART I

THE INORGANIC MATERIA MEDICA

GROUP I.—THE METALS, AMMONIUM, METALLOIDS AND NON-METALLIC ELEMENTS

SODIUM. SODIUM. Na. 23·00

THE official salts of Sodium and their preparations are derived mainly from Sodium Chloride. Sodium is a neutral ion, and has no specific effects: its salts owe their actions to their negative ions.

1. **Sodii Chloridum.**—Sodium Chloride. NaCl.

CHARACTERS.—Small, white, cubic crystals; taste saline. *Solubility.*—1 in 3 of water.

Preparations

1. **Injectio Sodii Chloridi.**—Normal Saline Solution. Sodium Chloride 0·9% in Water for Injection; sterilized.
2. **Injectio Sodii Chloridi Composita.**—Ringer's Solution. Sodium Chloride 0·86%, Potassium Chloride 0·03%, Hydrated Calcium Chloride 0·048% in Water for Injection; sterilized.
3. **Injectio Sodii Lactatis Composita.**—Ringer-Lactate Solution, Hartmann's Solution. Sodium Chloride 0·6%, Potassium Chloride 0·04%, Hydrated Calcium Chloride 0·04%, Lactic Acid 0·24% neutralized by Sodium Hydroxide; sterilized.

2. **Sodii Hydroxidum.**—Sodium Hydroxide. Caustic Soda. NaOH.

CHARACTERS.—White, fused sticks, very deliquescent and alkaline. *Solubility.*—1 in 1 of water.

3. **Sodii Carbonas.**—Sodium Carbonate. $Na_2CO_3,10H_2O$.

CHARACTERS.—Colourless rhombic crystals, efflorescent; taste strongly alkaline. *Solubility.*—1 in 2 of water.

Preparation

Sodii Carbonas Exsiccatus.—Exsiccated Sodium Carbonate. Na_2CO_3.

CHARACTERS.—A dry, white powder; taste strongly alkaline. An ingredient of Pilula Ferri Carbonatis.

4. **Sodii Bicarbonas.**—Sodium Bicarbonate. $NaHCO_3$.

CHARACTERS.—A white powder or small monoclinic crystals; taste saline. *Solubility.*—1 in 11 of water. 20 parts neutralize 16·7 parts of Citric Acid, or 17·8 parts of Tartaric Acid.

Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparations

1. **Injectio Sodii Bicarbonatis.**—5% in Water for Injection; sterilized.
2. **Tabellæ Sodii Bicarbonatis Compositæ.**—Soda Mint Tablets. 0·3 G (5 gr.) in each with Oil of Peppermint.
Dose.—2 to 3 tablets.

5. **Sodii Citras.**—Sodium Citrate. COONa.C(OH) $(CH_2.COONa)_2$, $2H_2O$.

CHARACTERS.—White, crystalline, slightly deliquescent powder; taste saline, neutral. *Solubility.*—1 in 2 of water.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparations

1. **Injectio Sodii Citratis Anticoagulans.**—Sodium Citrate 2·5%, Sodium Chloride 0·9%, in Water for Injection; sterilized.
2. **Injectio Sodii Citratis cum Dextroso.**—Sodium Citrate 2·5%, Dextrose 2·5% in Water for Injection; sterilized.
3. **Tabellæ Sodii Citratis.**—0·12 G (2 gr.) in each.

6. **Sodii et Potassii Tartras.**—Sodium Potassium Tartrate. Rochelle Salt. $(CHOH)_2COONa.COOK$, $4H_2O$.

CHARACTERS.—Colourless prisms; taste saline, neutral. *Solubility.*—1 in 1·5 of water.
Dose.—Metric, 8 to 16 G; Imperial, 120 to 240 gr.

Preparation

Pulvis Effervescens Compositus.—"Seidlitz Powder." No. 1. Sodium Potassium Tartrate, dry, 7·5 G; Sodium Bicarbonate, dry, 2·5 G; in *blue* paper. No. 2. Tartaric Acid, dry, 2·5 G; in *white* paper.
Dose.—Single: No. 1 dissolved in cold or warm water and No. 2 then added.

7. **Sodii Phosphas.**—Sodium Phosphate. $Na_2HPO_4,12H_2O$.

CHARACTERS.—Colourless, rhombic prisms, efflorescent, alkaline; taste saline. *Solubility.*—1 in 7 of water.
Dose.—Metric, 2 to 16 G; Imperial, 30 to 240 gr.

Preparation

Sodii Phosphas Exsiccatus.—Na_2HPO_4. A white, hygroscopic powder. *Solubility.*—1 in 15 of water.
Dose.—Metric, 0·6 to 5 G; Imperial, 10 to 75 gr.

8. **Sodii Sulphas.**—Sodium Sulphate. Glauber's Salt. Na_2SO_4, $10H_2O$.

CHARACTERS.—Colourless, monoclinic prisms, efflorescent; taste bitter, saline. *Solubility.*—1 in 3 of water.
Dose.—Metric, 2 to 16 G; Imperial, 30 to 240.

Preparation

Sodii Sulphas Exsiccatus.—Na_2SO_4. A white, hygroscopic powder. *Solubility.*—1 in 8 of water.
Dose.—Metric, 1 to 8 G; Imperial, 15 to 120 gr.

9. **Sodii Phosphas Acidus.**—Sodium Acid Phosphate. $NaH_2PO_4,2H_2O$.
CHARACTERS.—Colourless, rhombic crystals or crystalline powder; taste saline, acid. *Solubility.*—1 in 1 of water.
Dose.—Metric, 2 to 4 G; Imperial, 30 to 60 gr.

The other salts of Sodium are described under the acid radical.

ACTIONS AND USES

Sodium salts are divisible according to their actions thus: (1) *Sodium Chloride*; (2) *Antacids*: Carbonas and Bicarbonas; (3) *Saline Purgatives*: Sodii et Potassii Tartras, Sodii Phosphas and Sodii Sulphas; (4) *Sodium Citrate*; and (5) *Acid Sodium Phosphate.*

(1) **Sodium Chloride** is essential for the maintenance of the osmotic tension of the blood and tissues.

Externally.—Normal Saline Solution, 0·9 per cent. in sterile water, has no irritant properties and does not injure the cells because it is isotonic with the plasma. For these reasons it is valuable as a **lotion for wounds**, delicate mucous membranes such as those of the eye, mouth and nose, and for abdominal and other cavities. It has, however, no power of inhibiting bacterial growth. Hypertonic Saline Solutions, 5 per cent., inhibit bacterial growth and have been used as **antiseptics** on the ground that their hypertonicity withdraws water from the bacteria and also increases the flow of lymph and the diapedesis of phagocytes from the wounded tissues. They are effective in cleansing a dirty wound, boil, or carbuncle from debris by their osmotic action and solvent effect on proteins, but they possess little bactericidal action and are inclined to induce flabby granulations which bleed readily. Hypertonic Saline Solutions as **baths**, varying in strength from sea-water (3 per cent. NaCl) up to that of Nantwich or Droitwich (20 per cent.), produce a mild stimulation of the skin resulting in reflex stimulant effects. These are utilized very largely as general restoratives in convalescence, and in treating chronic rheumatic affections and certain skin diseases.

Saline Injections.—Severe hæmorrhage or surgical shock produces not only a fall in blood-pressure but, what is more serious, a rapid reduction in the plasma volume. Injectio Sodii Chloridi or, still better, Injectio Sodii Chloridi Composita (Ringer's Solution) are easy and effective means of **increasing the blood-volume** and pressure in such conditions, and in dehydration from acute diarrhœa, etc. In urgent cases they are given by intravenous or intraperitoneal injection, subcutaneous infusion or rectal injection in amounts of 1–2 pints (500–1,000 c.c.), warmed to 99°–105° F. If taken orally or given by rectal injection, their effect is more lasting because diuresis occurs slowly during some hours, whereas, if injected, the rise in the blood-volume lasts barely half an hour, because the fluid leaves the blood-stream rapidly, part being absorbed by the muscles and the remainder being excreted rapidly by the kidneys. Intravenous Saline Injections are, therefore, valuable in uræmia, diabetic coma, and alkaloidal poisoning, as they hasten excretion of poisons by the kidney. In order to overcome the disadvantage of their rapid excretion, they are now commonly given by continuous intravenous drips at the rate of 60 drops per minute (6–7 fl. oz. per hour) through a cannula into a convenient superficial vein (usually of the leg) and the drip may be maintained for a few days.

The addition to Normal Saline Solution of a colloid, such as 6 per cent. Gum Acacia, which exerts the same osmotic pressure as the blood colloids, retards the rate of diffusion into the tissues and of renal filtration, and **Gum Saline Solution** may be advisable when blood transfusion is impracticable.

Intravenous injections of 20–50 c.c. of **hypertonic** (30 per cent.) **Sodium Chloride solutions lower the pressure of the cerebro-spinal fluid.** They relieve, in from 5 to 10 minutes, headache associated with concussion, cerebral tumour and meningitis, and the effects last from one-half to two days; injections every third day maintain the improvement. This treatment also ameliorates the symptoms of cerebral hernia and decreases the size of the extrusion. Oral administration of 30 gr. thrice daily has a less marked effect. Conversely, **hypotonic saline** injections raise cerebro-spinal pressure and will relieve headache following withdrawal of spinal fluid. Hypertonic Ringer's Solution, containing 1·4 per cent. Sodium Chloride, given intravenously in amounts up to 5 pints, is valuable to relieve dehydration in cholera.

Internally.—Administered by mouth, small doses of Sodium Chloride are absorbed rapidly by the intestine and play their part in the maintenance of the **water and salt balance** of the tissues, which is regulated by the suprarenal cortical hormone and by vaso-pressin. In Addison's disease, doses of 225 gr. (15 G) of Sodium Chloride by mouth daily may be required to make good the deficiency of Sodium ions (see p. 216). In normal conditions, the administration of Sodium Chloride in dilute solution will produce **diuresis**; but after severe hæmorrhage or dehydration (anhydræmia) caused by persistent diarrhœa, fever or sweating, the deficiency of the blood in salt and water may have to be rectified by the administration of Sodium Chloride solutions orally, rectally, or intravenously. In œdemas associated with "Chloride retention," a **salt-free diet** may be effective in reducing the dropsy, and this has been tried with less success to lower blood-pressure in hyperpiesia.

When given orally, hypertonic solutions of Sodium Chloride produce osmotic effects, thus the mouth feels dry and the irritation of the gastric mucosa produces emesis reflexly; therefore a tablespoonful of salt dissolved in warm water is a safe and easily available **reflex emetic.** In the intestine hypertonic salt solutions do not cause diarrhœa as the Sodium Chloride is rapidly absorbed, but they increase the salt concentration of the tissues, provoke thirst and ultimately cause diuresis.

Administered as an enema Sodii Chloridum (1/2 oz. in 10 fl. oz. tepid water) is **anthelmintic** to Oxyuris vermicularis.

(2) **Antacid Group.**—The alkaline salts of Sodium owe their action to the dissociation of the hydroxyl ion. Their properties of (1) neutralizing acids, (2) forming soluble alkali albumins, (3) saponifying fats and (4) dissolving mucus, form the bases for their actions.

Externally.—The Hydroxide is occasionally used as a **caustic** to remove warts, since it abstracts the water and dissolves the proteins of the superficial cells, but, as the alkaline tissues cannot check its action, the necrosis may extend deeply and be painful and slow to heal.

Solutions of the Carbonate or Bicarbonate are **antidotes** to caustic acids, but the evolution of carbon dioxide may increase the pain. Dilute solutions (2 per cent.) of these salts, by saponifying fats and neutralizing irritant skin secretions, are useful **emollients and sedative** lotions for eczema, dermatitis and itching disorders, and they are also valuable to soften and remove scabs, crusts and callosities; for this reason, in extensive skin affections, alkaline baths are prescribed.

Internally.—In the *mouth* the antacids dissolve mucus, cleanse the epithelial surface, and neutralize the products of acid fermentation which often cause pain around the necks of the teeth. For these reasons the Bicarbonate (1–2) per cent. is a common ingredient of **mouth-washes** and **tooth-pastes.**

In the *stomach*, Sodium Bicarbonate, the preferable alkali, when given before meals has no important action on the gastric secretions. But, if given during, or after, meals, it first **lowers the**

acidity by neutralizing the hydrochloric acid and, about half an hour or more later, from the stimulant action of the carbon dioxide evolved, it causes a **hypersecretion** of gastric acid. These facts are important and, although Sodium Bicarbonate is a satisfactory **direct** antacid and largely used to relieve the discomfort of hyperacidity or acid fermentation and the pain of gastric ulcer, in the form of mixtures or as Soda Mint Tablets or in soda or Vichy water, the after-effect of hypersecretion must be borne in mind. Bicarbonates are particularly useful in chronic gastric catarrhs, where they may assist further by dissolving tenacious mucus on the mucous membrane, thus allowing freer access of the gastric juice to the food, and also by forming chlorides which aid the solution of proteins. Sodium Bicarbonate in emergency may be given for poisoning from mineral acids, but, as the evolution of carbon dioxide may rupture the eroded organ, hydrates or oxides are preferable.

The Carbonates, being converted into chlorides in the stomach, produce, even in small doses, a temporary lowering of the H-ion concentration of the plasma, i.e. a tendency to alkalæmia, and an **increase in the alkali reserve** (or bicarbonate-content) of the plasma. The surplus bicarbonate is, however, rapidly excreted by the kidney with the production of a less acid or an alkaline urine. This principle is utilized when full doses of Bicarbonates (5–10 G. per day) are administered as **remote antacids** to render the urine alkaline, either to aid in treating E.(B.) coli infections of the urinary tract, or to allay the irritation of the renal epithelium and vesical mucous membrane resulting from highly acid urines, e.g. in fevers like scarlatina, in nephritis, in vesical and urethral catarrhs and in uric acid diathesis. They may also retain some uric acid and urates in solution, but they do not dissolve uric acid or urate calculi, nor influence uric acid in the tissues. This method of treatment involves, however, interference with the efficiency of gastric digestion.

The value of Bicarbonates in raising the alkali reserve of the plasma is utilized to avert and treat **ketosis** which is due to defective carbohydrate metabolism and the consequent liberation of β-hydroxybutyric acid and aceto-acetic acid in the blood. Ketosis may arise from diabetes mellitus, starvation, infantile anorexia or vomiting from surfeit of fatty food, and commonly precedes fatty hepatic degeneration from Chloroform, Carbon Tetrachloride, Cinchophen and the organic arsenicals. Moderate degrees of ketosis can be treated by large doses of Sodium Bicarbonate or Citrate by mouth, but the symptoms of diabetic dyspnœa and coma may require to be relieved by the slow intravenous injection of 200–500 c.c. of the Injectio Sodii Bicarbonatis or Injectio Sodii Lactatis Composita.

Injectio Sodii Lactatis Composita, Ringer-Lactate or Hartmann's solution is isotonic and contains sodium lactate which is slowly converted in the body into Sodium Bicarbonate; it obviates the risk of producing alkalæmia. It is given intravenously as a rule, but may be given orally, for the treatment of diabetic coma and infantile gastro-enteritis.

Excessive doses of Carbonates can cause, through development of alkalæmia (alkalosis), symptoms of headache, vomiting, weakness, and, from reduction in the ionic calcium in the plasma, possibly tetany.

(3) The **Saline Purgative Group.**—Sodii et Potassii Tartras, Sodii Phosphas and Sodii Sulphas produce a characteristic purgative action in the small intestine owing to (1) *the relatively slow absorption* of the sulphate, phosphate or tartrate ions by the intestinal epithelium; (2) the consequent *retardation in the normal absorption of water* by the bowel; (3) the *drainage, by osmosis, of fluid from the tissues* into the intestine to restore the osmotic balance *if* the bowel contains a hypertonic solution of the salt; and (4) the *augmented peristalsis* resulting reflexly from the increased bulk of the intestinal contents. Doses given in a large bulk of water—the correct prescription—act wholly by retarding absorption of water. When the fluid contents reach the colon, this develops more active peristalsis, and, in from 1/2 to 2 hours, evacuation occurs of a stool, first of normal consistency and then of a profuse watery character, containing the large unabsorbed proportion (80 per cent.) of the saline purgative.

Large doses, given with little water, act by draining fluid from the tissues into the bowel in order to restore the osmotic balance in the intestine, but when given in concentrated solution, they may take 10 to 18 hours to cause purgation because time is required for the dehydration of the tissues.

Sodii Sulphas, which is a constituent of several sulphated mineral waters, including those of Leamington, Cheltenham, Marienbad and Karlsbad, is the most powerful of these purgatives; it produces a copious watery evacuation without griping. It is used as a routine purgative in chronic constipation, when it is best taken by sipping the dose dissolved in a tumblerful of tepid water before breakfast; or, in more concentrated solution, it removes œdematous fluid from the tissues, particularly in ascites from hepatic disease. The Phosphate and Sodium Potassium Tartrate are milder and less unpalatable, and are acceptable by children. The effervescing Seidlitz powder, administered in the morning, is a pleasant and rapid means of flushing out the alimentary canal and is often employed to complete the action of purgative pills. The value of these salts in catarrhal cholecystitis and in "biliousness" with constipation and high-coloured acid urine is due to their purgative action; they have no direct action in increasing the secretion of bile but in hypertonic solution may relax the biliary sphincter in the duodenum and drain the gall bladder.

Sodium Sulphate (4·3 per cent.) with Glucose (10 per cent.) in Normal Saline is given by continuous intravenous drip up to amounts of 500 Mils. in the treatment of anuria.

(4) **Sodium Citrate.**—Sodium Citrate is easily absorbed from the intestine, is converted into carbonates in the tissues, thus **raising the alkali reserve** of the plasma, and is excreted as bicarbonate, so making the **urine less acid, or alkaline.** It is used to treat acid intoxications—acidæmia and ketosis—particularly in children with persistent vomiting and acetone in the urine, and to treat the ketosis of diabetes mellitus, where doses up to 400 gr. (30 G) may be required to restore the alkali reserve. For urgent cases, Injectio Sodii Citratis cum Dextroso is given intravenously or, for children, Ringer-Lactate Solution.

Sodium Citrate is a useful **remote antacid** because it does not disturb gastric digestion like the bicarbonates; the dosage required to render the urine alkaline is about 150 gr. (10 G) daily. It is used to allay irritation from highly acid urines and in uric acid diathesis and to inhibit the growth of the Bacillus coli.

Added to **milk**, it precipitates the calcium salts and thus renders it less liable to clot in large curds; for this reason one Sodium Citrate tablet (2 gr.) is added per fluid ounce to milk for administration to infants and invalids.

Sodium Citrate 0·2 per cent. **prevents the coagulation of blood,** and it is now largely used in the technique of blood transfusion. The blood-group of the recipient having been ascertained and an appropriate or compatible donor selected, 420 c.c. of the donor's blood is removed and run into 120 c.c. of Injectio Sodii Citratis Anticoagulans (2·5 per cent), or better of Injectio Sodii Citratis cum Dextroso (each 2·5 per cent.) previously sterilized in a standard M.R.C. bottle, so that the blood-citrate mixture (540 c.c.) contains 0·55 per cent. of Sodium Citrate; the proportions vary slightly in different blood banks. The Dextrose acts as a preservative of the red cells and retards hæmolysis and, because a lower plasma *p*H also delays hæmolysis, some prefer to use Disodium Hydrogen Citrate (Sodii Citras Acidus, B.P.C.) in the same percentage instead of the official Trisodium Citrate. The Disodium Hydrogen Citrate also prevents caramelization of the Dextrose when heated in an autoclave. The citrated mixture is kept warm, and injected as soon as possible into a superficial vein of the patient's arm or leg. Reactions of chill and slight fever from half an hour to four hours after injections of citrated blood are not uncommon but are rarely serious. Blood transfusion (*see* p. 509) is now successfully employed to restore blood-volume and pressure, and to provide hæmoglobin, after severe hæmorrhage, e.g. after operations or child-birth, in severe anæmias, purpura hæmorrhatica, gastric ulcer, icterus neonatorum and in carbon monoxide poisoning.

The injection of Sodium Citrate, 10–50 Mils of a 10 per cent. solution, intravenously, shortens the coagulation time, probably by injuring the platelets and liberating thromboplastin; this is said to be useful in hæmophilia.

(5) Acid Sodium Phosphate.—This, the normal acid salt of the urine, is readily absorbed from the intestine and is excreted unchanged by the kidney; it therefore **increases the acidity of the urine slightly** and on this basis is used as a urinary antiseptic, but Ammonium Chloride is much more efficient. It is useful if the urine is only slightly alkaline, and is less successful in coccal infections with highly ammoniacal urine. It was formerly given prior to Hexamine. Doses above 75 gr. (5 G) per day may cause diarrhœa. It has also been tried in oxaluria for its solvent action on calcium oxalate.

POTASSIUM. POTASSIUM. K. 39·10

The Potassium ion is a *muscular depressant*, but, although the salts retain this characteristic, they are, when given orally, absorbed and excreted so rapidly that the acid radical alone determines their respective actions; except as diuretics, sodium salts are equally efficient.

1. **Potassii Chloridum.**—Potassium Chloride. KCl.

CHARACTERS.—White cubical crystals or powder; taste saline. *Solubility.*—1 in 3 of water.

2. **Potassii Hydroxidum.**—Potassium Hydroxide. Caustic Potash. KOH.

CHARACTERS.—Hard, white, deliquescent pencils, very alkaline, and corrosive. *Solubility.*—1 in 1 of water; 1 in 3 of alcohol 90%.

Preparation

Liquor Potassii Hydroxidi.—Liquor Potassæ. Solution of Potash. 5% of KOH in water.

CHARACTERS.—A colourless, very alkaline fluid; feeling soapy.

3. **Potassii Bicarbonas.**—Potassium Bicarbonate. $KHCO_3$.

CHARACTERS.—Colourless, monoclinic prisms, slightly alkaline; taste saline. *Solubility.*—1 in 4 of water. 20 parts neutralize 14 parts of Citric Acid, or 15 parts of Tartaric Acid.
Dose.—Metric, 1 to 2 G; Imperial, 15 to 30 gr.

4. **Potassii Citras.**—Potassium Citrate. $COOK.C(OH)(CH_2.COOK)_2, H_2O$.

CHARACTERS.—White, granular, deliquescent crystals or powder; taste saline. *Solubility.*—1 in 1 of water.
Dose.—Metric, 1 to 2 G; Imperial, 15 to 30 gr.

5. **Potassii Acetas.**—Potassium Acetate. $CH_3.COOK$.

CHARACTERS.—White, foliaceous, satiny masses, or granular particles, very deliquescent, slightly alkaline; taste saline, sharp. *Solubility.*—2 in 1 of water.
Dose.—Metric, 1 to 2 G; Imperial, 15 to 30 gr.

6. **Potassii Nitras.**—Potassium Nitrate. Nitre. Saltpetre. KNO_3.

CHARACTERS.—Striated 6-sided prisms, or white crystalline masses; taste cool, saline. *Solubility.*—1 in 4 of water.
Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

7. **Potassii Tartas Acidus.**—Acid Potassium Tartrate. Purified Cream of Tartar. $(CHOH)_2COOK.COOH$.

CHARACTERS.—A white, gritty powder or crystalline fragments; taste pleasant, acid. *Solubility.*—1 in 220 of water.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

8. **Potassii Chloras.**—Potassium Chlorate. $KClO_3$.

CHARACTERS.—Colourless, monoclinic crystals; taste cool, saline. May explode if rubbed with sulphur, sulphides or organic matter. *Solubility.*—1 in 16 of water; 1 in 30 of glycerin. *Incompatible* with ferrous salts, tannic acid and oxidizable substances, e.g. sugars.
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparation

Tabellæ Potassi Chloratis.—0·3 G (5 gr.) in each.

The other salts of Potassium are described under the acid radical.

ACTIONS AND USES

Externally.—Potassium Hydroxide is powerfully **caustic**; it saponifies the fatty secretion of the skin, extracts water from the cells, and dissolves the superficial layers as alkali-albumins. It is apt to penetrate deeply and cause ulceration, since the tissues, being alkaline, cannot limit its action. Liquor Potassii Hydroxidi is used to remove epithelium, scabs, etc., to soften corns and ingrowing toe-nails. Like the Sodium alkalis, dilute solutions of the Hydroxide or Bicarbonate allay itching of the skin, and, being **antacids**, neutralize caustic acids on the skin: they are also antiseptic and cleansing, and are used for this purpose with Olive Oil in the form of soft soaps.

Internally.—In the *mouth*, Potassium Hydroxide, 0·5 per cent., is a useful solvent for adherent protein debris, mucus, and "fur" in stomatitis. Potassium Chlorate is alleged to liberate oxygen in contact with inflamed tissues and thus to act as an antiseptic; its saline taste excites salivation and the Chlorate is excreted by the oral mucous glands. It is used as an **oral antiseptic** in aphthous and mercurial stomatitis, tonsillitis, and pharyngitis as tablets (5 gr.) or, in 2 per cent. solution, as a gargle or spray; it is often prescribed with Borax, Sodium Bicarbonate, and—in painful cases—Cocaine. In toxic doses, Chlorates can convert oxyhæmoglobin into methæmoglobin which is excreted in the urine: this may occur from excessive use of the tablets.

In the *stomach* Liquor Potassii Hydroxidi may be used as an **antidote** to acid poisoning, and, freely diluted, it is preferable to carbonates, since no carbon dioxide is evolved. Given before meals, Potassium Bicarbonate dissolves mucus and, after meals, it acts as a **direct antacid.** But, in most cases, in the treatment of dyspepsia the Sodium or Magnesium alkalis are better.

In the *intestine* Potassium Acid Tartrate is a **saline purgative,** producing in from one-half to two hours a watery motion, but being more easily absorbed it is not so powerful as the Sodium salts. In ascites from renal or hepatic disease, the Acid Tartrate is particularly useful, since it combines purgative and diuretic properties. It may be given in a lemonade (Imperial Drink), 60 gr. in a pint, made with citric acid, saccharin, lemon and water to relieve thirst in fevers and diabetics.

Potassium salts are absorbed rapidly into the blood, but since they are rapidly excreted their effects are transitory. Potassium Chloride may have to be given to cases of Addison's Disease under treatment with Deoxycortone Acetate. The Carbonate and Bicarbonate directly increase the alkali reserve of the plasma: and it must be noted that the Citrate, Tartrate, and Acetate after absorption are converted by oxidation into bicarbonates also, and are excreted as such. The value of alkalis in uric acid diathesis and gout is still undetermined. The pathology of these conditions is doubtful, and there is no conclusive evidence that Potassium salts increase the excretion of uric acid.

The Potassium ion is essential for contractile tissues; in small amounts (0·03 per cent.) it serves to maintain the normal contractility by promoting muscular relaxation, therefore it is contained in Ringer's Solution for Injection. Potassium Chloride, 12 G in water orally, aborts attacks of familial periodic paralysis. Potassium salts, when injected, are **depressants towards muscular, nervous and cardiac tissues,** but, being rapidly excreted, they never by oral administration cause untoward symptoms from such actions.

Diuretic and Remote Antacid Actions.—Potassium salts are excreted very rapidly, chiefly by the kidneys, and this speedy elimination renders them particularly suitable as **saline diuretics.** Because they are easily absorbed, they pass into the plasma and increase its osmotic tension; this effect is rectified by fluid of lower osmotic tension being drawn from the tissues into the blood, which thus becomes more hydræmic. When the blood reaches the renal glomeruli, the salts and water filter out, and in the tubules, owing to the raised osmotic tension and the presence of a "low threshold" salt, the normal reabsorption of water from the urine into the blood is diminished; hence the urinary water is increased and the tissue fluids are reduced. Potassium Acetate, Citrate, Acid Tartrate and Bicarbonate are diuretics—their relative efficiency being in the order named. They are employed chiefly in renal and hepatic dropsy, in febrile illness, and as adjuvants to such remedies as Digitalis and Squill in cardiac dropsy. The organic salts do not irritate the renal tissues and may safely be prescribed in nephritis but, when much of the excretory organ is damaged, a correspondingly lessened effect must obviously be anticipated. Potassium Nitrate also has diuretic properties, as it is a very easily absorbed salt, but it is apt to cause irritation of the kidneys.

Potassium Acetate, Citrate, Bicarbonate, and to a lesser extent the Acid Tartrate, are excreted as carbonates and bicarbonates, and are therefore powerful but transitory **alkalinizers of the urine.**

The organic salts have the advantage that they do not neutralize gastric acidity like the Bicarbonate. They are used to render the urine alkaline in uric acid gravel and acute or chronic gout: but, to maintain alkalinity, full and repeated doses must be given. They are useful to inhibit the growth of E.(B.) coli in the urine, to allay renal and vesical irritation and frequency of micturition due to high urinary acidity. They may hold some uric acid in solution and, although they do not dissolve calculi, they may cause their disintegration by dissolving the mucus which holds the particles of the calculus together. The waters of Bath, Buxton, Kissingen, Karlsbad, Contrexéville and Vichy contain traces of Potassium salts, and are in repute for the treatment of gravel.

Respiratory passages.—As stated under Sodium, the action of the alkalis as **expectorants** is not established. Potassium Nitrate fumes relieve some cases of asthma: absorbent paper is soaked in a solution of Nitre, dried and ignited, and the fumes are inhaled; or cigarettes impregnated with the salt may be used and the smoke inhaled.

Lithium Carbonate (*not official*), **Dose.**—0·12 to 0·3 G (2 to 5 gr.), a direct antacid, and **Lithium Citrate, Dose.**—0·3 to 0·6 G (5 to 10 gr.), a remote antacid, used to have a reputation in the treatment of the uric acid diathesis and gout because lithium biurate is more soluble than sodium biurate; but to displace the sodium ion, Lithium salts would have to be in toxic concentration in the tissues: therefore, their use is irrational.

AMMONIUM. AMMONIUM. NH_4. 18·04

Preparations containing free Ammonia possess stimulant properties, the results of reflex actions.

1. Liquor Ammoniæ Fortis.—Strong Solution of Ammonia. NH_3, 32·5% by weight, dissolved in water.

CHARACTERS.—A colourless, strongly alkaline liquid; odour very pungent. Sp. gr. 0·880.

Preparations

1. **Liquor Ammoniæ Dilutus.**—Liquor Ammoniæ. NH_3, 10% by weight, dissolved in water.

CHARACTERS.—Colourless liquid; odour and taste pungent.

Dose.—Metric, 0·6 to 1·2 Mils; Imperial, 10 to 20 min., well diluted.

2. **Spiritus Ammoniæ Aromaticus.**—Aromatic Spirit of Ammonia, Spirit of Sal Volatile. Strong Solution of Ammonia, 6·0; Ammonium Bicarbonate, 2·5; with Oils of Lemon and Nutmeg in 90% Alcohol, 75; and water to 100.

CHARACTERS.—Colourless liquid; odour and taste pungent, aromatic.
Dose.—Metric, 1 to 4 Mils; Imperial, 15 to 60 min.

3. **Linimentum Camphoræ Ammoniatum.**—Ammoniated Liniment of Camphor. Strong Solution of Ammonia 25%; Camphor, 12·5%; with Oil of Lavender in 90% Alcohol.

2. Ammonii Bicarbonas.—Ammonium Bicarbonate. Sal Volatile NH_4HCO_3.

CHARACTERS.—White hygroscopic crystals, odour and taste slightly ammoniacal, pungent. *Solubility.*—1 in 5½ of water.
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.
If Ammonium Carbonate is prescribed, Ammonium Bicarbonate shall be dispensed.

3. Ammonii Chloridum.—Ammonium Chloride. Sal Ammoniac. NH_4Cl.

CHARACTERS.—Colourless, hygroscopic crystals; inodorous, taste saline, cooling. *Solubility.*—1 in 3 of water. *Incompatible* with alkalis.
Dose.—Metric, 0·3 to 4 G; Imperial, 5 to 60 gr.

4. Liquor Ammonii Acetatis Fortis.—Strong Solution of Ammonium Acetate. Contains about 57% of CH_3COONH_4.

CHARACTERS.—Syrupy liquid; odour acetous and ammoniacal; taste sharp, saline.
Dose.—Metric, 1 to 4 Mils; Imperial, 15 to 60 min.

Preparation

Liquor Ammonii Acetatis Dilutus.—Dilute Solution of Ammonium Acetate. Mindererus' Spirit. Contains about 7% of CH_3COONH_4.
CHARACTERS.—Colourless liquid; odour acetous, taste sharp, saline.
Dose.—Metric, 8 to 30 Mils; Imperial, 1/4 to 1 fl. oz.

ACTIONS AND USES

Externally.—Liquor Ammoniæ Fortis, like other alkalis, will act as a caustic to the skin, especially if evaporation be prevented. Liquor Ammoniæ Dilutus is applied to neutralize stings of ants but is useless for those of bees or wasps.

When weaker solutions are applied as liniments to the skin, they penetrate the cells and irritate the superficial tissues and cutaneous nerves, causing pain, and, by an axon reflex, dilating the vessels in the area to which they are applied; a **rubefacient** action. From more prolonged application the irritation may induce a flow of lymph from the vessels and tissues, so that blistering (**vesication**) results. At the same time the irritation of the cutaneous nerves leads reflexly to vascular and trophic changes in neighbouring organs—a **counter-irritant** effect (*see* p. 573).

Ammonia is used as a **local circulatory stimulant** and **counter-**

irritant in the form of Linimentum Camphoræ Ammoniatum in acute and chronic inflammation of joints—lumbago, fibrositis, etc.—as well as in bronchitis and pleurisy.

Inhaled by the nose, the vapour of Ammonia or the Bicarbonate (smelling salts) is a powerful **local and, reflexly, a general stimulant.** The pungent sensation causes a watery secretion from the nose, conjunctivæ and mouth, sneezing is induced, and the irritation of the sensory nerves leads reflexly to stimulation of respiration and circulation. Inhalation of Ammonia often checks hiccough.

Internally.—Liquor Ammoniæ Dilutus, Ammonium Bicarbonate, and Spiritus Ammoniæ Aromaticus, given well diluted, are **antacids** in the stomach and have a **carminative** action which relieves flatulence, but, owing to their irritant action, they are rarely used as ingredients of alkaline stomachic mixtures in atonic dyspepsia and debility, and only when a stimulant action on the gastric wall is desirable.

In moderate doses, Ammonium Bicarbonate, and the Liquores Ammonii Acetatis, by moderate and sustained irritation of the sensory vagal endings in the gastric mucosa, produce such reflex effects as increased salivation, increased secretion of bronchial mucus and moderate sweating. They are, therefore, useful as **reflex expectorants and diaphoretics.** The Liquors of Ammonium Acetate, being milder in action, are employed, chiefly in diaphoretic mixtures, in order to encourage sweating and thus to lower temperature in the treatment of fevers in children, or of colds and influenza in adults. Ammonium Bicarbonate induces reflexly a more copious and liquid mucous secretion from the bronchi and is useful in treating subacute and chronic bronchitis, broncho-pneumonia, and the resolution stage of lobar pneumonia.

By similar action in irritating sensory endings, Ammonium Bicarbonate and Spiritus Ammoniæ Aromaticus are valuable **reflex general stimulants.** For this effect the ammoniacal vapour may be inhaled or they may be given as a single dose by mouth, when the irritation of the nasal or gastric mucosa leads reflexly to stimulation of the higher cerebral centres: and at the same time, reflexly through the medulla, the respirations are increased in rapidity although often shallower, the heart beats more quickly and strongly, and the blood-pressure is raised somewhat. On the other hand, the inhalation of too strong Ammonia vapour causes reflex respiratory and cardiac inhibition and a fall in blood-pressure. For their effects as reflex general stimulants, Ammonium Bicarbonate and Spiritus Ammoniæ Aromaticus are largely used to restore consciousness, circulation and respiration in fainting from nervous or physical exhaustion, and as a "first aid" in asphyxia from drowning, etc. This stimulant action is a desirable accompaniment of their effect as expectorants in pulmonary infections where the increased pulmonary ventilation and increased vigour of cough are valuable.

Larger doses of Ammonium Bicarbonate—1 to 2 G (15 to 30 gr.)—produce reflexly, from gastric irritation, prompt **emesis.** They cause a sensation of warmth in the stomach, salivation and nausea, preceding the evacuation of the gastric contents, but usually produce little nervous depression.

Actions after absorption.—Ammonium Acetate and Bicarbonate are absorbed rapidly, and soon converted by the liver into urea: $2CH_3.COONH_4 + 4O_2 = (NH_4)_2CO_3 + 3CO_2 + 3H_2O$; and $(NH_4)_2CO_3 = CO(NH_2)_2 + 2H_2O$. The Acetates, having larger doses, are, by the formation of urea, mild and non-irritant **diuretics,** and are useful in fevers, ascites and nephritis; they have *no* renal antacid effects.

Ammonium Chloride.—This gives off no free Ammonia and has therefore none of its irritant or reflex actions.

Given by mouth, Ammonium Chloride is absorbed rapidly and in the liver the Ammonium ion is converted through its carbonate into urea; the chloride ion thus liberated unites with some of the basic ions in the plasma and so lowers the alkali reserve; to rectify this, an increase of acid salts is excreted by the kidney; excessive dosage may cause acidæmia. In consequence, Ammonium Chloride **increases the acidity of the urine** and thus acts as a **urinary antiseptic.** Doses of 10 gr. given in cachets, because of its nauseating taste, six to eight times daily will lower the pH of the urine to about 5·5 which is necessary to assist Mandelic Acid or Hexamine therapy in pyelitis; smaller doses may suffice as antiseptics in treating alkaline cystitis.

Ammonium Chloride acts as a **diuretic** partly by its conversion to urea and partly by lowering the alkali reserve; it increases the effect of the Mercurial diuretics, and doses up to 8 G (120 gr.) are usually given during two days prior to treatment of cardiac œdema by Injectio Mersalyli. It is also given as a diuretic prior to the Quinidine treatment of auricular fibrillation.

The use of Ammonium Chloride as an expectorant has no rational basis.

Ammonium Nitrate and Ammonium Phosphate.
Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr. These salts, like Ammonium Chloride, act as diuretics, lower the alkali reserve of the plasma and make the urine more acid. The Phosphate is the least nauseating of the three.

CALCIUM. CALCIUM. Ca. 40·08

The Calcium ion has important physiological actions. It is essential for the coagulation of blood and the curdling of milk; and, in balanced proportions with Sodium, Potassium and Magnesium, for the molecular changes which are associated with excitability and rhythmic functions of muscle; it also decreases the permeability of cell membranes and its salts give rigidity to bones and teeth.

1. **Calcii Hydroxidum.**—Calcium Hydroxide. Slaked Lime. $Ca(OH)_2$.
CHARACTERS.—A white powder, strongly alkaline. *Solubility.*—Cold water (1: 900); more so with sugar (1: 60).

Preparation

Liquor Calcii Hydroxidi.—Solution of Lime. Lime Water. Contains 0·15% of Calcium Hydroxide or about 2/3 gr. in 1 fl. oz.
CHARACTERS.—Colourless liquid; taste, alkaline.
Dose.—Metric, 30 to 120 Mils; Imperial, 1 to 4 fl. oz.

2. **Creta.**—Prepared Chalk. Native Calcium Carbonate. $CaCO_3$.
CHARACTERS.—White friable masses or a white insoluble powder.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparations

1. **Pulvis Cretæ Aromaticus.**—Aromatic Powder of Chalk. Prepared Chalk 25% with Cinnamon, Nutmeg, Clove, Cardamom, and Sucrose.
CHARACTERS.—A yellowish-brown powder; taste, aromatic.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.
2. **Pulvis Cretæ Aromaticus cum Opio.**—Aromatic Powder of Chalk with Opium. Opium 2·5% in Aromatic Powder of Chalk 4 G (60 gr.) contains 0·01 G (1/7 gr.) Morphine.
CHARACTERS.—A brown powder; taste, aromatic, narcotic.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.
3. **Hydrargyrum cum Creta.**—*See* Hydrargyrum p. 86.

3. **Calcii Carbonas.**—Precipitated Calcium Carbonate. Precipitated Chalk. $CaCO_3$.
CHARACTERS.—A white, micro-crystalline, insoluble powder.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

4. **Calcii Chloridum.**—Calcium Chloride. $CaCl_2$.
CHARACTERS.—White, very deliquescent masses; taste, bitter, acid. *Solubility.*—1 in 1·5 of water; 1 in 3 of alcohol 90% *Incompatible* with carbonates, phosphates, tartrates and sulphates.

Doses.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.
For injections, Hydrated Calcium Chloride should be used.

5. **Calcii Chloridum Hydratum.**—Hydrated Calcium Chloride. $CaCl_2, 6H_2O$.

CHARACTERS.—Colourless, odourless, deliquescent crystals; taste, bitter. *Solubility.*—1 in 0·25 of water.
Doses.—*By intravenous injection:*
Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

6. **Calcii Gluconas.**—Calcium Gluconate. $[CH_2OH.(CHOH)_4.COO]_2Ca,H_2O$.

CHARACTERS.—A white crystalline, tasteless powder. *Solubility.*—1 in 30 of water, slowly.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparation

Injectio Calcii Gluconatis.—Calcium Gluconate. 10% in Water for Injection.
Dose.—*By intravenous or intramuscular injection:*
Metric, 10 to 20 Mils; Imperial, 150 to 300 min.

7. ***Calcii Lactas.***—*Calcium Lactate.* $Ca(COO.CHOH.CH_3)_2,5H_2O$.

CHARACTERS.—A white powder; almost tasteless. *Solubility.*—1 in 18·5 of water; easily in hot water.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparation

Tabellæ Calcii Lactatis.—0·3 G (5 gr.) in each.

8. **Calcii Phosphas.**—Calcium Phosphate. $Ca_3(PO_4)_2$.

CHARACTERS.—A light, amorphous insoluble powder.
Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

Calx Chlorinata is described under Chlorine. Calcium Mandelate under Mandelic Acid.

ACTIONS AND USES

Externally.—Calcium Oxide is **caustic** and combined with Caustic Potash (Vienna Paste) was formerly used for this purpose. It is also a **disinfectant** and the practice of lime-washing out-houses has this advantage. Emulsions of equal parts of Lime Water and Olive Oil (Carron Oil) were formerly popular sedative applications for burns. Chalk, the amorphous Carbonate, in the form of a dusting powder is antacid, physically **protective**, and desiccative (drying) and is used, either alone or combined with starch, an astringent or an antiseptic, to absorb exudations and allay irritation from moist eczemas and ulcers. Chalk is the basis of many cosmetic powders.

Internally.—In the *mouth*, Calcii Carbonas, which is slightly gritty, is an **antacid and abrasive dentifrice** and forms the chief constituent of most tooth powders and pastes.

In the *stomach:* (1) the Hydroxide, Carbonates and Lime Water act as direct **antacids** and reduce gastric acidity. Lime Water is frequently used in the acid dyspepsias and vomiting of infants, particularly as a diluent for milk, when it prevents the rennin from curdling the milk in clumps. When dilution of the milk is undesirable, a saccharated solution of lime is used or Sodium Citrate added. For older children, the Pulvis Cretæ Aromaticus is a suitable preparation for hyperacidity and fermentative dyspepsia. (2) The insoluble Calcium salts have in full doses a **sedative action** on the gastric mucosa by acting as mechanical protectives prior to their conversion into Calcium Chloride. (3) Calcium Hydroxide and Lime Water are valuable **antidotes** in poisoning by mineral acids, alkaloids or oxalates; a readily available form is "whiting," which should be given freely with water.

In the *intestine,* much of the Calcium Chloride, formed in the stomach, will be precipitated again in the form of insoluble Carbonate. The absorption of Calcium salts is therefore slow, and the Carbonate will form a **protective** coating over the intestinal mucosa and decrease reflex peristalsis. For this reason, Calcium salts are apt to be constipating and are used in the treatment of the moderate diarrhœas due to indigestible foods or intestinal toxæmias in children. The Pulvis Cretæ Aromaticus, which contains carminatives to allay griping, is often used, or, if a more powerful sedative effect be desired, Pulvis Cretæ Aromaticus cum Opio may be prescribed. In such cases the **adsorptive capacity** of the particles of insoluble Carbonate for bacterial toxins is of important value.

Assimilation of Calcium.—Calcium salts are absorbed slowly from the bowel and only to the extent of about 25 per cent.; unless required by the tissues most of the absorbed Calcium is excreted, partly as phosphates by the urine but largely (75 per cent.) through the large intestine. A normal person requires 0·5 G of Calcium daily, but during pregnancy and lactation, for the needs of the infant, and during adolescence, the bodily need for Calcium salts is greater.

Tissue and Bone Calcium.—Although lack of lime salts in the food may produce Calcium deficiency in the tissues, the cause of this is more commonly defective absorption and utilization of Calcium owing to lack of Vitamin D, which promotes the absorption of Calcium and Phosphorus in balanced proportions, probably by reducing intestinal alkalinity and lessening the formation of unabsorbable Calcium salts and soaps. The most frequent result of deficient Calcium absorption and metabolism is **improperly calcified bone** (rickets) **and imperfectly calcified, or perhaps malformed, teeth** in children. These conditions can be prevented or remedied by ensuring an adequate supply of Calcium and Vitamin D in the diet. Most naturally this may be achieved by augmenting the ration of whole milk and eggs, but the administration of Calcium salts and Cod Liver Oil may be essential. In this connection the pre- and post-natal care of mothers must not be overlooked, because during pregnancy and lactation the infant relies on the mother for its legacy of Calcium, and a **deficiency in the maternal tissues** during these periods may presage defective dentition in the child and predispose both mother and child to dental caries and nervous excitability.

Blood Calcium.—The plasma contains 10 mg per cent. of Calcium, of which about 6–7 mg per cent. is in ionized form, the remainder in combination with protein. The maintenance from the store in osseous tissue of the proportion of Calcium in the blood is the function of the parathyroids. Administration of parathyroid promotes the transfer of Calcium from the bony tissues to the blood, raises the total blood Calcium, augments for one or two days the proportion of ionic Calcium to colloidal (inert) Calcium in the plasma and increases its excretion.

Since Calcium ions are necessary for the conversion of prothrombin into thrombin, it was thought that deficient Calcium was the cause of retarded coagulation of the blood in hæmophilia, etc., and, therefore, Calcium Chloride, Lactate (well diluted), or Gluconate (which is not a gastric irritant) has been given in doses of 15 gr. thrice daily in this and allied conditions, e.g. hæmoptysis, intestinal hæmorrhage and purpura hæmorrhagica. The treatment does increase the amount of Calcium available in the tissues and blood, but it is doubtful whether this accelerates materially the coagulation of blood. In some of these conditions the platelets are more at fault than the blood Calcium. Although critical tests afford conflicting evidence, many surgeons are persuaded from clinical experience that the administration of Calcium salts does **accelerate the coagulation time.** Injectio Calcii Gluconatis, when given intramuscularly, is painless and, in 5 per cent. or 10 per cent. solution, it is more satisfactory for intravenous administration than Hydrated Calcium Chloride. These have been used when severe hæmorrhage was anticipated, e.g. prior to parturition, and clinical successes are recorded.

A reduction below normal of the ionic blood Calcium produces hyperexcitability of nervous and muscular tissues, e.g. **tetany**; this may arise either from defective assimilation, as in rickets, from persistent vomiting, from excision or disease of the parathyroid, or from excessive administration of bicarbonates by mouth or by injection. These symptoms are relieved at once by an intravenous injection of Hydrated Calcium Chloride, or by Injectio Calcii Gluconatis intravenously or intramuscularly, and more slowly by giving Calcium salts by mouth. Conversely, excessive ionic Calcium **depresses nervous excitability** and injections of Calcium salts have been used, with variable success, in spasmodic conditions, such as paralysis agitans, chorea and hypocalcæmic convulsions in children. A high calcium proportion in the blood is also valuable in the prevention and treatment of the toxic effects of Carbon Tetrachloride, and Calcium Gluconate is commonly given before it.

In osteomalacia there is defective Calcium assimilation associated with a high excretory rate, and the blood Calcium has to be maintained at the expense of the bones, which consequently become spongy; large doses of Calcium salts are helpful in association with Vitamin D. The blood calcium is usually low in sprue and this should be remedied.

Calcium ions **diminish the permeability of cell membranes** such as the capillary endothelium, and experimentally it has been shown that local injections can restrict inflammatory œdemas. Oral administration of the Chloride, Lactate, or Gluconate and, in severe cases, intramuscular doses of Injectio Calcii Gluconatis are used effectively in the treatment of serum sickness or rashes and also, with less reliability, for the relief of urticaria, erythema, purpura, chilblains, angio-neurotic œdemas, vaso-motor catarrhs, and reactions from injections of metallic preparations.

Diuretic Action.—Calcium Chloride, when given by mouth, is precipitated largely as the carbonate and phosphate in the intestine, but, since the Chloride ion is absorbed, there results a tendency towards acidæmia. This contributes to the ultimate production of **diuresis and increased acidity of the urine**. Calcium Chloride may be used as a diuretic in nephritis, especially if the urine be alkaline, and, if given during a few days previously, it enhances the action of mercurial diuretics in relieving œdemas. If given frequently, however, it causes enteritis. The diuretic effects of calcareous waters like those of Bath and Contrexéville are essentially due to the amount of water taken.

Other Uses of Calcium Salts.—Based on the fact that healing of tuberculous lesions in the lung is associated with calcification, Calcium Salts have been widely tried in **phthisis**; reports as to their efficacy are, however, not convincing. The symptoms of **chronic lead poisoning** are relieved by intravenous injection of 10 c.c. of 10 per cent. Hydrated Calcium Chloride, which locks up the lead in the bones.

Because Calcium salts excite the contractility and raise the tone of cardiac muscle, they have been used by mouth and intravenously to improve the tone of the heart and arterioles, but, as the action of Digitalis is potentiated by Calcium, its salts should not be injected while patients are under Digitalis treatment. Nauheim Baths, which contain Calcium salts with free Carbon Dioxide, were regarded as useful in cardiac failure, but the benefit which followed was essentially due to the stimulation of the respiratory centre by the Carbon Dioxide and the régime of massage and exercises which followed the baths.

Calcium Lævulinate $Ca(C_5H_7O_3)_2,2H_2O$ containing 13·1% Calcium, may be given orally, intramuscularly or intravenously in doses of 2 G (30 gr.) three or four times daily in 10% solution. **Calcium Sodium Lactate** is less irritant to the stomach than Calcium Lactate and is often substituted for the latter in similar dosage.

Calx Sodica.—Soda Lime. A mixture of Sodium and/or Potassium Hydroxides with Calcium Hydroxide.

CHARACTERS.—White or greyish-white granules of specific size and hardness; they may be coloured by an indicator (phenolphthalein, potassium permanganate or methyl violet) to show when the absorptive capacity for Carbon Dioxide is exhausted. Soda Lime absorbs 20% of its weight of CO_2

ACTIONS AND USES

Soda Lime is used to absorb Carbon Dioxide in closed-circuit anæsthetic inhalers; the size of the granules is stipulated so as to avoid small ones impeding respiration and large ones being inefficient absorbents. One pound of Soda Lime in a closed inhaler suffices for two or three hours and, in conversion to the carbonate, generates heat, which, if it does not rise above 40° C. (104° F.), is advantageous. If a saturated container is set aside, the Soda Lime will partly recover in an hour and may be used again, the total serviceability being about eight hours. Soda Lime must not be used with Trichlorethylene; this it decomposes into dichloracetylene which produces nerve paralyses.

MAGNESIUM. MAGNESIUM. Mg. 24·32

The purgative effect of the Magnesium ion is determined by its slow absorption from the bowel. When injected, the Magnesium ion depresses the excitability of the whole of the nervous system.

1. **Magnesii Carbonas Ponderosus.**—Heavy Magnesium Carbonate. $3(MgCo_3)$, $Mg(OH)_2$, $4H_2O$.

CHARACTERS.—A white, granular, almost insoluble powder.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.

Preparation

Magnesii Oxidum Ponderosum.—Magnesia Ponderosa. Heavy Magnesia. MgO.
CHARACTERS.—A white powder; insoluble in water.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.

2. **Magnesii Carbonas Levis.**—Light Magnesium Carbonate. $3(MgCO_3)$, $Mg(OH)_2$, $4H_2O$.

CHARACTERS.—A very light, white, insoluble powder, mainly amorphous but with prismatic crystals. It has 3½ times the bulk of the Heavy Carbonate.
Dose.—Metric ,0·6 to 4 G; Imperial, 10 to 60 gr.

Preparation

Magnesii Oxidum Leve.—Magnesia Levis. Light Magnesia. MgO.
CHARACTERS.—A white, very light, insoluble powder, 3½ times the bulk of Heavy Magnesia.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.

3. **Liquor Magnesii Bicarbonatis.**—"Fluid Magnesia." $Mg(HCO_3)_2$. The Bicarbonate in solution saturated with Carbon Dioxide.

CHARACTERS.—A clear, slightly effervescing fluid. Contains about 1 G of Carbonate in 60 Mils (7½ gr. in 1 fl. oz.).
Dose.—Metric, 30 to 60 Mils; Imperial, 1 to 2 fl. oz.

4. **Mistura Magnesii Hydroxidi.**—Cream of Magnesia. An aqueous suspension containing 8·25% of hydrated Magnesium Oxide, $Mg(OH)_2$ and also Light Magnesium Oxide (5·25%).

CHARACTERS.—A white suspension; taste, slightly alkaline and bitter. Contains about 0·9 G of Oxide in 16 Mils (12½ gr. in 240 min.).
Dose.—Metric, 4 to 16 Mils; Imperial, 60 to 240 min.

5. **Magnesii Trisilicas.**—Magnesium Trisilicate. Hydrated Magnesium Silicate, 2Mg0, $3Si0_3$.

CHARACTERS.—A white, tasteless, insoluble powder.
Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

6. Magnesii Sulphas.—Magnesium Sulphate. Epsom Salt. $MgSO_4$, $7H_2O$.

CHARACTERS.—Small, colourless, rhombic prisms; taste saline and bitter. *Solubility.*—1 in 1·5 of water.

Dose.—Metric, 2 to 16 G; Imperial, 30 to 240 gr.

Preparations

1. **Magnesii Sulphas Exsiccatus.**—$MgSO_4$. A white powder. *Solubility.*—1 in 2 of Water.
Dose.—Metric, 2 to 12 G; Imperial, 30 to 180 gr.
2. **Mistura Sennæ Co.**—Contains 25%. (*See* p. 171.)

ACTIONS AND USES

Externally.—Magnesium Silicate (French Chalk or Talc) is used as a **dusting powder**, as an ingredient of cosmetic preparations, and as a lubricant for massage. Magnesium Carbonates and Oxides are occasionally used as protectives for skin diseases and ulcers. A 10 per cent. solution of Magnesium Sulphate relieves pain and itching if applied locally to inflamed surfaces and has been recommended as an application for erysipelas and painful wounds. Exsiccated Magnesium Sulphate 2, made into a paste with Glycerin 1, is applied on lint as a lymphagogue antiseptic for boils and carbuncles.

Internally.—In the *mouth*, the Magnesium Oxides and Carbonates are abrasive **antacid dentifrices**; they effectively relieve pain due to acid fermentation and, as their insoluble particles adhere around the necks of the teeth, the action is more prolonged than that of the soluble alkalis. The Mistura Magnesii Hydroxidi is useful as an antacid mouth wash for such conditions. Magnesium Peroxide is an oxidizing antiseptic used, when diluted with 5–10 parts of Chalk, as a tooth powder.

In the *stomach*, Magnesium preparations are (1) useful **antidotes**; the Oxides, preferable as they do not evolve carbon dioxide, and the Carbonates neutralize mineral acids, form insoluble salts with oxalates, mercuric, cupric and arsenical salts, and precipitate alkaloids from their salts. The Sulphate will precipitate the soluble salts of Lead and Barium.

(2) The Oxides and Mistura Magnesii Hydroxidi are valuable **antacids** because they are more efficient in neutralizing excessive acidity in the stomach than bicarbonates or carbonates, which, owing to the stimulant action of the carbon dioxide they evolve, tend to provoke subsequent hyperacidity. The Magnesium alkalis are given before meals in order that the insoluble salts may form a protective coating over the gastric mucosa and neutralize hyper-

acidity following the ingestion of food. When the after-effects of carbon dioxide upon the stomach are desired, the Carbonates or Liquor Magnesii Bicarbonatis are employed. These alkaline salts of Magnesium are also frequently prescribed after meals as powders—or suspended with mucilage as mixtures—along with Bismuth Carbonate or Sodium Bicarbonate in the **treatment of hyperacidity**, chronic gastric catarrh and gastric ulcer. Thus, powders containing Magnesia and Sodium Bicarbonate alternating with ones containing Calcium Carbonate and Sodium Bicarbonate (0·6 G (10 gr.) of each ingredient) are given half an hour after the two-hourly milk feeds in Sippy's treatment for gastric and duodenal ulcer. As the Magnesium Oxides and Carbonates are converted in the stomach into the soluble Chloride, they eventually act as saline purgatives; therefore, if the Magnesia powders cause undesirable purgation, a change is made to those containing Calcium Carbonate, which are constipating, and *vice versa*. Overdosage with alkalis may, however, lead to alkalosis.

Magnesii Trisilicas is particularly valuable as an antacid, protective and adsorbent in hyperacidity and gastric ulcer, because its antacid action is prolonged and it does not cause alkalosis, as it is converted into magnesium chloride and colloidal silica. Tribasic Magnesium Phosphate, 4 G (60 gr.) is also used to obviate alkalosis.

In the *intestine*, Magnesium salts act as **saline purgatives** because the Magnesium ions are not easily absorbed and, as the sulphate ion is also more slowly absorbed than other anions, Magnesium Sulphate is the most effective of the salines. The purgative action is due to the fact that the soluble Magnesium salts, being unabsorbed, maintain the osmotic tension of the bowel contents and prevent the normal absorption of water. If they are given *in dilute solution* (2 to 5 per cent.) they prevent the absorption of the large bulk of water in which they are dissolved, and the distension of the bowel by the fluid arouses reflex peristalsis which rapidly transmits the liquid contents through the intestine, and evacuation occurs, in from one-half to two hours after the dose, of a stool, at first solid and later liquid, containing the bulk of the Magnesium salt; the action is not accompanied by any pain or griping. When intended to flush out the bowel in this way, the dose, dissolved in a tumblerful of water, should be sipped about half an hour before breakfast.

If administered *in concentrated solution* (10 to 25 per cent.) Magnesium Sulphate—or other salines—will so raise the osmotic tension in the bowel that fluid will be drawn from the tissues into the intestine to adjust the osmotic balance. That this is so is shown by the fact that such solutions temporarily increase the relative number of erythrocytes by withdrawing fluid from the plasma. But as the transudation takes time, purgation may not occur until 12–18 hours after the dose. This method of administration is useful when it is desired, as in œdema, to drain fluid from the tissues. Magnesium Sulphate is frequently given as a routine purgative in the form of Mistura Sennæ Composita, in which the Senna acts as a synergist by stimulating colonic peristalsis, as the "Mistura Alba" of hospitals, which contains Magnesium Carbonate, 10 gr., Magnesium Sulphate, 60 gr. in 1 fl. oz. of peppermint water; or also in the form of aperient waters, containing Magnesium and other sulphates, like Cheltenham, Hunyadi Janos, etc. These natural waters have, however, no real advantage over artificial imitations.

Magnesium Sulphate, like other saline purgatives, may be used in a single large dose to effect a rapid clearance from the bowel of indigestible food, poisons and toxins; the prevention of absorption by the raised osmotic pressure is here important and explains the value of saline purgatives in poisoning from drugs which are not easily soluble in water. Single large doses are also used to empty the bowel in febrile illness but are more effective when preceded by Calomel or one of the anthracene purgatives, given on the previous evening.

In small doses, repeated every morning, Magnesium Sulphate is a valuable aperient in chronic constipation; mild cases respond well to administration of the Carbonates or Liquor Magnesii Bicarbonatis but, if there be marked flatulence, the Oxides or Mistura Magnesii Hydroxidi should be chosen. For children suffering either from slight constipation, or from diarrhœa arising from indigestible or fermented food and associated with symptoms of acidosis, the Oxides and Mistura Magnesii Hydroxidi are particularly suitable, while a single dose of Pulvis Rhei Compositus (containing 66 per cent. of the Carbonates) is an effective initial purgative in such cases.

Hypertonic solutions of Magnesium Sulphate in the duodenum, by relaxing the sphincter of Oddi and contracting the gall bladder, cause expulsion of the bile, and from 1 to 2 fl. dr. of a 25 per cent. solution in an ounce of water is given in the morning for the treatment of catarrhal cholecystitis. Hypertonic solutions given as an enema (6 fl. oz. of a 25 per cent. solution) or by intramuscular or intravenous injection (10 to 20 Mils. of a 10 per cent. solution) are effective means of lowering intraspinal and intracranial pressure, of relieving headache following intraspinal anæsthesia, and in assisting recovery from cerebral thrombosis; they are less liable to cause œdema than hypertonic saline or sucrose.

Absorption and Excretion of Magnesium Salts.—Magnesium salts are absorbed very slowly and are excreted rapidly, hence when given orally they do not usually raise the Magnesium content of the plasma. They are excreted as chlorides in the urine but do not influence its amount. In the presence of gross renal disease, the Magnesium ion is not readily excreted and the Magnesium in the plasma may rise considerably and produce drowsiness or even coma. Sodium Sulphate is to be preferred to Magnesium Sulphate in these circumstances.

Injections of Magnesium Salts.—If injected intravenously, Magnesium Sulphate depresses the cerebrum and the spinal reflex centres, and later paralyses the myoneural junctions of motor nerves; therefore, it can check convulsions and relax muscles. Injections intramuscularly or intravenously of 10 to 20 c.c. of a 10 per cent. solution of Magnesium Sulphate have been used with success as sedatives in maniacal excitement, in eclampsia, and to check convulsions in tetanus and uræmia. The hypertonic solution also lowers intracranial pressure. From 2·5 to 5 c.c. of a 25 per cent. solution may also be injected intraspinally or intracisternally for tetanus, but, as this controls the convulsions only, antitetanic serum must be used. The danger of these injections is the proximity of the effective to the lethal dose, but an equivalent dose of Calcium Chloride acts as an antidote.

BARIUM. BARIUM. Ba. 137·36

1. **Barii Sulphas.**—Barium Sulphate. $BaSO_4$.

CHARACTERS.—A heavy, white, insoluble powder; odourless and tasteless.

Dose (*not official*).—**Metric, 60 to 150 G; Imperial, 2 to 5 oz.**

ACTIONS AND USES

Barium stimulates directly cardiac, involuntary, and voluntary muscular tissue. When administered orally, **Dose.**—0·016 to 0·12 G (1/4 to 2 gr.), Barium Chloride **increases the excitability, rate and tone of the cardiac muscle** and contracts the arterioles; thus it causes a gradual but sustained rise in blood-pressure which reflexly may later slow the cardiac rhythm. It also augments the movements and tone of involuntary muscles; thus vomiting and purging with colic are induced. Barium Chloride has been tried with doubtful benefit in cardiac weakness, and has been advised in the treatment of the syncopes of the Adams-Stokes syndrome.

Barium Sulphate is very insoluble and therefore not toxic. It is used in the form of **Barium Meals** (2 to 5 oz. in from 5 to 15 fl. oz. of cornflour or other "food") to render the intestinal tract impervious to X-rays for the diagnosis of intestinal disorders, or it may be injected into sinuses (20 per cent. in Olive Oil) so that their track may be discovered.

Barium Sulphide, 10 to 25 per cent., with soap, starch, etc., to form a paste, is the basis of many *depilatories*; it may irritate the skin, if left on for more than five minutes.

BISMUTHUM. BISMUTH. Bi. 209·0

The insoluble Bismuth salts are mechanical protectives and sedatives. When injected, the metal is toxic to the spirochæte of syphilis.

1. **Bismuthi Carbonas.**—Bismuth Oxycarbonate. $(Bi_2O_2CO_3)_2, H_2O$.

CHARACTERS.—A heavy, whitish, insoluble powder; odourless and tasteless. *Incompatible* with iodides.
Dose.—Metric, *0·6 to 2 G*; Imperial, 10 to 30 gr.

Preparation

Trochiscus Bismuthi Compositus.—Contains in each lozenge 0·15 G (2½ gr.) of Bismuth and Heavy Magnesium Carbonates and 0·3 G (5 gr.) of Calcium Carbonate.

2. **Bismuth Oxychloridum.**—Bismuth Oxychloride. BiOCl.

CHARACTERS.—A white amorphous or crystalline powder; insoluble and tasteless; a basic salt of varying composition containing 80% Bi.
Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.
By intramuscular injection:
Metric, 0·06 to 0·2 G; Imperial, 1 to 3 gr.

Preparation

Injectio Bismuthi Oxychloridi.—Bismuth Oxychloride 10% with Dextrose 5% and Chlorocresol 0·2% in Water for Injection; dispensed in sterile glass ampoules and sterilized. 30 min. contains 3 gr. of Bismuth Oxychloride.
Dose.—*By intramuscular injection:*
Metric, 1 to 2 Mils; Imperial, 15 to 30 min.

3. **Bismuthi Salicylas.—Bismuth Salicylate. Bismuth Oxysalicylate. $C_6H_4OH.COO.BiO$.**

CHARACTERS.—A white or nearly white, insoluble powder; odourless and tasteless.

Dose.—Metric 0·6 to 2 G; Imperial, 10 to 30 gr.
By intramuscular injection:
Metric, 0·06 to 0·2 G; Imperial, 1 to 3 gr.

Preparation

Injectio Bismuthi Salicylatis.—Bismuth Salicylate 10% with Camphor and Phenol 1% in Arachis Oil. Sterilized. Dispensed in sterile glass ampoules or phials; 20 min. contains 2 gr. of Bismuth Salicylate.

Dose.—*By intramuscular injection:*
Metric, 0·6 to 1·2 Mils; Imperial, 10 to 20 min.

4. **Bismuthum Præcipitatum.**—Precipitated Bismuth.

CHARACTERS.—A dull-grey, insoluble powder which diffuses in water; its particles are less than 15 microns in diameter.

Dose.—*By intramuscular injection:*
Metric, 0·06 to 0·2 G; Imperial, 1 to 3 gr.

Preparation

Injectio Bismuthi.—"Bismostab." Precipitated Bismuth 20% with Dextrose 5% and Chlorocresol 0·1% as antiseptic in Water for Injection. Dispensed in sterile glass ampoules or phials; 15 min. contains 3 gr. of Bismuth.

Dose.—*By intramuscular injection.*
Metric, 0·5 to 1 Mil; Imperial, 8 to 15 min.

5. **Bismuthi et Sodii Tartras.**—Sodium Bismuthyl Tartrate.

CHARACTERS.—A white powder or yellow scales. *Solubility.*—1 in less than 1 of water; *neutral.*

Dose.—*By intramuscular injection:*
Metric, 0·06 to 0·2 G; Imperial, 1 to 3 gr.

Preparation

Injectio Bismuthi et Sodii Tartratis.—60 mg in 1 Mil (1 gr. in 15 min.) of Water for Injection.

Dose.—*By intramuscular injection:*
Metric, 1 to 3 Mils; Imperial, 15 to 45 min.

6. **Bismuthi Subgallas.**—Bismuth Subgallate. Dermatol.

CHARACTERS.—A yellow, odourless, insoluble powder.

Preparation

Suppositoria Bismuthi Subgallatis.—0·3 G (5 gr.) in each.

ACTIONS AND USES

Externally.—Applied in the form of dusting powders or ointments (5 to 30 per cent.) Bismuth Carbonate and the Oxychloride (pearl-white) are cosmetic **protectives** to the skin against the detrimental effects of wind, or sunlight. If the skin be inflamed or raw, as in chapped hands, cracked nipples, eczema or pruritus ani, the Carbonate or Oxychloride in ointment form with Zinc Oxide, Lanolin and Lard is an effective protective and **sedative** which relieves itching. Insoluble Bismuth Salts are also used with success as **dusting powders** in catarrhs of accessible mucous membranes.

Bismuth Carbonate or Subnitrate 1, Iodoform 2, Liquid Paraffin q.s. to make a thick paste ("Bipp") was formerly used as an **antiseptic** for wounds and sinuses. Bismuth Subgallate is used as a dusting powder for wounds but it has little astringent or antiseptic value. The suppositories are used for hæmorrhoids.

Internally.—In the *stomach,* insoluble Bismuth Salts have **protective and sedative** actions by forming over the mucous membrane an insoluble coating which protects it from irritation. They must be *given before meals* in order to coat the mucosa uniformly and *in full dose* since the action is purely mechanical. Bismuth Carbonate, which is a weak **antacid,** is largely used in the treatment of hypertonic dyspepsia or gastric catarrh resulting from a surfeit of food or alcohol and may be prescribed with the Carbonates of Magnesium and Calcium and Sodium Bicarbonate, in the powders used for the "intensive alkaline" treatment of gastric or duodenal ulcer. It may also be combined with carminatives or an Opium preparation if flatulence or pain be a prominent symptom. For mild degrees of hyperacidity and ambulant cases the Trochiscus Bismuthi Compositus is a useful antacid. The nervous or reflex vomiting of hysteria and pregnancy is alleviated by Bismuth Carbonate.

In the *intestine* the **protective and sedative** influence of the insoluble Bismuth Salts upon the mucosa renders them valuable remedies **for diarrhœa**; the insoluble particles are also **useful by adsorbing toxins** and preventing their absorption. Bismuth Salicylate is decomposed in the intestine into Bismuth Carbonate or Oxide and Salicylic Acid. Thus, it exerts not only a protective effect here but also a slight **antiseptic** action. A mixture containing equal doses of the Carbonate and Salicylate along with Tinctura Chloroformi et Morphinæ (B.P.C.) is, as a sedative and carminative, highly effective in subacute gastro-enteritis. In lienteric diarrhœa, Bismuth salts are beneficial, and they may be used as adjuvants during convalescence from amœbic or bacillary dysentery and from giardia (lamblia) infections. It should be remembered that the Bismuth salts are converted finally into the Sulphide in the bowel and this imparts to the fæces a black colour which may be mistaken for blood.

The passage of X-rays is obstructed by the salts of Bismuth but they are more expensive than Barium Sulphate and seldom used.

Absorption of Bismuth Salts.—Bismuth salts are absorbed only in minute amounts from the intestine; these are excreted through the kidney and large intestine without producing any symptoms. More rapid absorption may occur if they are applied to large wounded surfaces, e.g. burns; and poisoning, characterized by loss of appetite, salivation, buccal ulceration, gastro-enteritis and nephritis, may ensue.

Bismuth Therapy in Syphilis.—Intramuscular injections of soluble double salts or suspensions of insoluble preparations of Bismuth have proved of great value in the treatment of syphilis.

Technique.—Bismuth injections are given intramuscularly, by means of a glass syringe, deeply into the muscles of the upper and outer third of the buttock; preliminary aspiration should be tried to ensure that the point of the needle has not punctured a vein. The dose is injected slowly and the part massaged so as to distribute the fluid. As regards choice of preparations, the Injectio Bismuthi, and the Injectio Bismuthi Oxychloridi, watery suspensions, are rather more rapidly absorbed and excreted than the Injectio Bismuthi Salicylatis, which is suspended in oil. Sodium Bismuthyl Tartrate, a *neutral* salt, may be given suspended (5 per cent.) in oil; by this method it is less painful and less rapidly absorbed and excreted than when dissolved (6 per cent.) in Water for Injection; this is also a powerful diuretic.

The exact routine of *dosage* varies; most clinics administer 0·1 to 0·2 G Bismuth at weekly intervals; others give 0·1 to 0·2 G at intervals of four days. The course is usually interrupted by periods of rest so that ten doses are spread over three months, and the total amount injected during a course varies between 2·0 and 3·0 G. Penicillin and Neoarsphenamine injections are also given and details of a course of treatment are given on p. 101. In infants with congenital syphilis, doses *equivalent to 0·02 G of* Bismuth may be injected once a week (*see* p. 103).

Effects of Bismuth Therapy.—Bismuth therapy in syphilis may be assessed generally as less efficacious but more lasting than that of Penicillin or the organic arsenicals and much better than mercurial treatment. Penicillin and Neoarsphenamine are more effective and act more rapidly in primary syphilis In tertiary and congenital syphilis, Bismuth is safer than arsenicals. Under Bismuth therapy alone, spirochætes disappear in three or four days from the primary lesion and chancres heal rapidly; the blood is generally free after two injections. In secondary syphilis the skin rashes and mucous lesions speedily clear, while in tertiary syphilis cutaneous nodules and gummata retrogress after three or four injections. Bismuth therapy, if commenced early in conjunction with Arsenic, decreases the incidence of neurosyphilis. Bismuth is preferable to Arsenic or Mercury if nephritis or cardiac disease be present, or if jaundice supervenes on Neoarsphenamine administration. Bismuth therapy is useful in lupus erythematosus and, with Neoarsphenamine injections, in yaws.

Toxic Effects of Bismuth Injections.—The safety margin of Bismuth is higher than that of Mercury, and toxic effects are therefore less frequent and severe. The early signs of overdose are salivation, stomatitis, a fœtid breath, and the appearance of a dark line on the gums and dark spots on the buccal mucosa. Such symptoms occasionally appear after 0·8 G Bismuth and are not infrequent after 2·5 G have been given. The symptoms of severe poisoning are ulcerative stomatitis, headache and depression, enteritis and hepatitis. Mouth washes are used to avert stomatitis. Further injections are postponed until the symptoms improve. Toxic effects are treated by Dimercaprol.

PLUMBUM. LEAD. Pb. 207·21

Lead salts are typical metallic astringents, acting by precipitating proteins.

1. **Plumbi Monoxidum.**—Lead Oxide. Litharge. PbO.
   CHARACTERS.—Light-red, heavy, insoluble scales or powder.

2. **Plumbi Acetas.**—Lead Acetate. Sugar of Lead. $Pb(CH_3COO)_2, 3H_2O$.
   CHARACTERS.—Small white prisms or crystalline masses; odour acetous, taste sweet, astringent. *Solubility.*—1 in 2·5 of water (slightly acid). *Incompatibles.*—Sulphates, iodides, vegetable astringents and opium preparations.
   Dose.—Metric, 0·03 to 0·12 G; Imperial, 1/2 to 2 gr.

3. **Liquor Plumbi Subacetatis Fortis.**—Strong Solution of Lead Subacetate. Goulard's Extract. $Pb_2O(CH_3COO)_2$.
   CHARACTERS.—A colourless, alkaline, astringent liquid, becoming turbid. Contains about 42·5% Lead Subacetate.

Preparation

Liquor Plumbi Subacetatis Dilutus.—Goulard's Lotion. The Strong Liquor 1·25% in Distilled Water, freshly prepared.

ACTIONS AND USES

Externally.—Solutions of Lead salts are powerful **astringents** and **sedatives** upon wounds and exposed mucous membranes. Their actions are: (1) They precipitate the proteins in the albuminous exudates which cover inflamed tissues or mucous membranes, thus forming an insoluble pellicle which remains as a protective coating on the affected surface. (2) They precipitate the proteins in the protoplasm of the superficial cells, and thus check serous exudations and secretion of mucus and retard cellular proliferation. (3) They may restrict circulation in the superficial capillaries by precipitating the albumins of their walls and of their supporting tissues. By these means Lead reduces inflammatory reactions. Lead Acetate and Subacetate cause much less smarting than other metallic astringents, because the Acetic Acid released by the union of Lead with the protein is less irritant, but the Liquor Plumbi Subacetatis Fortis may exert a caustic and irritant action and cause sloughing and death of the cells; it is only used after dilution with 20 or 30 volumes of water. The Dilute Subacetate Solution is employed as an astringent application on lint to ulcers, eczema, and acute inflammatory and itching skin affections, chilblains, bruises, bed-sores and granulating surfaces; and as a lotion for chronic inflammatory discharges from the vagina, urethra and ear (1 in 40 of the Dilute Solution, or 1 in 250 of Lead Acetate). Lead salts should not be used as astringents for conjunctivitis because opacities may occur if the cornea be ulcerated. An ointment made with 12·5 per cent. of the Strong Solution of Lead Subacetate or 4 per cent. Lead Acetate relieves itching from external hæmorrhoids and pruritus ani. Soluble preparations of Lead may also be applied as **hæmostatics** in capillary bleeding.

Internally.—The astringent action of Lead is exerted upon the *mouth* and throat: a pellicle of precipitated albumin forms on the mucous membrane ; the secretions are reduced; a feeling of dryness is experienced; and inflammation, where present, is controlled. The Dilute Subacetate Solution with Glycerin, as a gargle or paint, is sometimes used in the treatment of tonsillitis and pharyngitis.

In the *stomach* similar effects are produced: albumins of the food are precipitated; the secretions and vascularity of the mucosa are diminished; hence the soluble Lead salts may cause indigestion.

In the *intestine*, the mucous membrane becomes coated with precipitated protein; this lessens mucous secretion, and protects the wall from irritation so that peristalsis is reduced; the precipitation of food-proteins renders the contents more solid, and the delayed transmission, resulting from these two effects, allows more time for absorption of water; thus **constipation** results. To increase its constipating action, Lead Acetate is sometimes given in pill form with Opium for the treatment of obstinate diarrhœa. Lead Acetate gr. 1 with Cocaine Hydrochloride gr. 1/4 as a suppository is an effective astringent and surface anæsthetic for internal hæmorrhoids.

Absorption and Excretion.—Lead salts are absorbed slowly from the bowel, and pass into the blood, and from it chiefly to the liver, kidneys and bones. Excretion is slower than absorption, hence cumulation and chronic poisoning occur. Most of the lead is excreted through the large intestine, and smaller amounts through the kidneys and bile.

Actions after Absorption.—The specific actions of Lead may best be appreciated by a description of the symptoms of poisoning due to the metal. As acute poisons, Lead salts in large doses act purely as astringents and intestinal irritants, causing nausea, vomiting, great thirst, abdominal pain with constipation, and finally collapse. Magnesium Sulphate should be given to precipitate the Lead salt and remove it.

Chronic Lead Poisoning, or "Plumbism," is still common in persons working in Lead. Early symptoms are pallor, nausea, loss of appetite, and constipation. A sweet metallic taste persists in the mouth, the breath is fœtid, and chronic thirst is complained of. During the constipation, "lead colic," referred to the umbilicus, occurs in paroxysms; it is due to spasmodic contractions of the intestine from a tonic action of the metal on the muscular coats, and relief is afforded by pressure on the area. Following these early symptoms, a blue line develops on the gums from conversion of the Lead in the submucous tissues into the sulphide, the sulphur being derived from the tartar of the teeth. Anæmia soon becomes evident, and examination reveals the presence of punctate basophilia; the destruction of erythrocytes is often followed by jaundice and high-coloured urine; and the accompanying symptoms are lassitude, weakness, and, in women, amenorrhœa. The pulse is usually slow and the blood-pressure increased. At a later stage there occur paralyses, due to peripheral neuritis, of certain groups of the voluntary muscles, particularly those of the extensor aspect of the forearm excepting the brachioradialis, and the characteristic "wrist drop" results. Amblyopia from optic neuritis and cerebral symptoms (Lead encephalopathy) may occur; sensory disturbances, anæsthesia, and arthralgia are not common. Finally, interstitial nephritis and general arteriosclerosis ensue and prove fatal. Lead is an active abortifacient; in early pregnancy, it may cause fœtal death by a necrosis of the chorion or in late stages act as an ecbolic by causing tonic contractions of the uterus.

In chronic poisoning Magnesium Sulphate is given as a purgative and Potassium Iodide, which dissolves Lead Albuminate, is given to augment the excretion, but the solution of the Lead deposited in the bones may aggravate the symptoms. More controllable are the effects of giving an acid-forming salt such as Ammonium Chloride together with Parathyroid Extract; by this method Lead is gradually removed from the bones and excreted. If during treatment colic or other symptoms of plumbism increase, they can be rapidly suppressed by the reverse procedure of giving Calcium Lactate or alkalis orally in order to lock up the Lead again in the bones, or by an injection of Calcium Gluconate intravenously in urgent cases.

Thallium Acetate (*not official*).—CH_3COOTl.

Dose—0·008 G per Kg (2/35 gr. per lb.) body weight.

ACTIONS AND USES

Thallium Acetate has been used as a temporary **depilatory** in children under the age of ten years suffering from ringworm of the scalp. A single dose only should be given, preferably as a tablet of the exact dosage. A week later the hair is brittle, falls during the next two weeks and restoration occurs in about six weeks. Depilation involves all bodily hair innervated by the sympathetic. Liquor Iodi Mitis is used to treat the infected areas.

The treatment involves considerable risk: even from a single dose gastro-enteritis may occur; or, after a week's delay, stomatitis, diarrhœa and peripheral neuritis, e.g. pains, muscular weakness and tremors, may develop; or from excessive doses degenerative changes in the endocrine organs and metabolic disturbances may be produced.

ARGENTUM. SILVER. Ag. 107·88

Silver salts are *antiseptic*, *astringent* and *caustic*.

Argenti Nitras.—Silver Nitrate. $AgNO_3$. Lunar Caustic.

CHARACTERS.—Colourless tabular prisms; taste bitter, metallic. *Solubility*.—2 in 1 of water.

Preparation

Argenti Nitras Induratus.—Toughened Caustic. Made by fusing Silver Nitrate, 95, and Potassium Nitrate, 5.

CHARACTERS.—White or greyish-white, thin, cylindrical pencils, very brittle; soluble in water.

ACTIONS AND USES

Externally.—When Silver Nitrate or Argenti Nitras Induratus is applied to the skin, it absorbs water from the superficial cells and sweat glands, is dissolved, and precipitates the proteins of *the epithelial cells. Death of the cells results from this astringent* action and the toxicity of the Silver ion, the eschar becoming black by the reduction of silver albuminate by light. This **caustic** action causes some pain and an inflammatory reaction of the *deeper skin layers, and the area separates as a slough, but healing* follows rapidly. Silver Nitrate cannot penetrate deeply, because silver albuminate is insoluble in sodium chloride, which salt also precipitates any excess of silver. It is, therefore, an excellent caustic for warts, condylomata, granulations, small septic punctures or bites, etc., and for pharyngeal ulcers and small growths in the larynx. For the former conditions, the moistened Argenti Nitras Induratus pencil may be applied to the area; for the latter, a small piece of the pencil fused on the end of a silver probe should be used, lest the pencil be broken and swallowed.

Solutions of the Nitrate, when applied to the broken skin or to mucous membranes, act like Lead, but are more irritant and less astringent. Silver precipitates the proteins and chlorides of the plasma and discharge, and of the protoplasm of the superficial cells. Solutions of 1 in 1,000 are only weak **astringents**, but are very active **antiseptics** because the Silver ion has a specific toxic action on bacteria and also precipitates their proteins. Strengths of 2 to 5 per cent. may be used for ulcers and granulations; as an eye-wash for corneal ulcer, strengths of 0·2 to 0·5 per cent.; and in conjunctivitis, gonorrhœal ophthalmia, and in prophylaxis of ophthalmia neonatorum, drops of 0·5 to 1 per cent. As urethral and vaginal injections, strengths of 0·05 to 0·1 per cent. are usually employed, while for pruritus a 1 per cent. solution is useful. A 5 per cent. solution in Spiritus Ætheris Nitrosi hardens the skin and is used in certain skin diseases and to prevent bed-sores.

Internally.—In the *mouth* Silver Nitrate exerts its astringent effects, but these are rapidly annulled owing to its precipitation by the chlorides and proteins. In strengths of 0·25 to 1 per cent.

it is a useful gargle in tonsillitis, and a paint (2 to 5 per cent.) for pharyngitis and relaxed sore throat. Gargles of Silver Nitrate are efficacious in checking the tobacco habit; no taste of silver persists in the mouth, but, on smoking, an unpleasant metallic taste arises—due no doubt to excretion of Silver.

Reaching the *stomach,* Silver Nitrate is precipitated by the hydrochloric acid and mucus, and does not act as an irritant. An enema (0·2 per cent. in distilled water) is of value in chronic dysenteric ulceration of the bowel.

Only a small portion of the Silver ingested is absorbed, and, *in chronic poisoning, it is deposited in insoluble form as granules* in the organs, connective tissues and skin, giving the last a dusky slate-blue colour—*argyria.* On the gums a blue line is formed. Silver has no influence on the tissues. Such chronic poisoning is *now rarely seen.*

ORGANIC SALTS OF SILVER

The organic and colloidal preparations of Silver form two groups: (*a*) those which liberate the toxic Silver ion rapidly and are proportionally rapid bactericides and irritating, and (*b*) those which ionize slowly and have a less active but more prolonged antiseptic action, and a negligible irritant action.

Argentoproteinum.—Silver Protein. "Protargol." "Argein."

CHARACTERS.—A brown, hygroscopic, odourless powder, prepared with gelatin and containing about 8% of Silver. *Solubility.*—1 in 2 of water.

ACTIONS AND USES

Silver Protein is not astringent but, as it ionizes with moderate rapidity, it is slightly irritant; it has a more prolonged although much less powerful antiseptic action than Silver Nitrate. It is used as an antiseptic for stomatitis, tonsillitis, conjunctivitis, and ophthalmia neonatorum in 2 to 10 per cent. solutions; and for acute gonorrhœa, urethral and bladder irrigation, and as enemata in dysentery and colitis, solutions of 0·25 to 1 per cent. are suitable.

Collargol, containing 70 per cent. Ag., is used as an ophthalmic antiseptic (1 to 5 per cent. solutions) and for gonorrhœa, cystitis, pyelitis, and colitis.

Argenti Proteinas Mite.—(B.P.C.) Mild Silver Protein. Silver Vitellin. Silver Nuclein.

CHARACTERS.—A brown powder or black scale, soluble in water, containing from 20 to 25% of Silver.

ACTIONS AND USES

Mild Silver Protein is not astringent and ionizes slowly, therefore it is not irritant and is a weaker antiseptic than Silver Protein. It is used for ophthalmic antiseptic purposes in 25 to 50 per cent. solutions, and for acute urethritis, cystitis, and vaginitis in 5 to 10 per cent. solutions.

Albargin, containing 15 per cent. Ag., is used in 1 to 3 per cent. injections for gonorrhœa; and *Argyrol*, containing 20 per cent. Ag., is used as a conjunctival antiseptic. *Collosol Argentum*, 0·5 per cent. Ag., is used undiluted as an antiseptic on sensitive tissues.

AURUM. GOLD. Au. 197·2

Sodii Aurothiomalas.—Sodium Aurothiomalate.

CHARACTERS.—A pale-yellow, hygroscopic, and very soluble powder.

Dose.—*By intramuscular injection weekly:*

Metric, 10 mg. increasing gradually to 100 mg.; Imperial, 1/6 gr. gradually increasing to $1\frac{1}{2}$ gr.

Preparation

Injectio Sodii Aurothiomalatis contains 10 mg. in 1 Mil (1/6 gr. in 15 min.) of Water for Injection.

ACTIONS AND USES

The mode of action of Gold salts is unknown. Gold was formerly used as Sodium Aurothiosulphate (Sanocrysin) in pulmonary tuberculosis by about twelve weekly intravenous injections of a 5 per cent. solution. The initial injections usually caused some focal pain, temporary increase in cough and a febrile reaction. Some few cases improved temporarily in weight and condition, in physical signs and radiographically, but they later retrogressed and the results were very disappointing; severe reactions were common.

Sodium Aurothiomalate (Myocrisin) is given by intramuscular injection as a 10 per cent. or 50 per cent. solution in dose of 10 mg. at first and, if this is tolerated, then 50 mg. and 100 mg. weekly for ten weeks (usual total 1 G.). It is used, after a rest during the acute stage, in treating rheumatoid arthritis, particularly when the blood-sedimentation rate is high. Improvement, including a fall in the blood-sedimentation rate, occurs in a high percentage of cases by the end of the first course, and is shown by improved health, relief from joint pains, and softening of the swellings. Further courses, separated by intervals of about three months, are desirable to maintain and increase improvements. Lupus erythematosus is often greatly benefited and the lesions sometimes healed by Gold injections. Other Gold compounds used similarly are Allochrysine, Krysolgan, Lopion, Parmanil, and Solganal.

Toxic Effects.—Serious reactions from Gold injections are common: severe febrile reactions; skin eruptions (erythematous and papular) lead to exfoliative dermatitis; stomatitis, vomiting, diarrhœa, jaundice and toxic hepatitis may occur; albuminuria and nephritis, purpura, aplastic anæmia, leucopenia and agranulocytosis.may also develop. Reactions can be reduced by giving 10 c.c. of 10 per cent. Calcium Gluconate intramuscularly or by giving Sodium Thiosulphate orally, but Dimercaprol (B.A.L.) injections (*see* p. 383) are much more effective antidotes.

ZINCUM. Zinc. Zn. 65·38

The Zinc ion is *antiseptic* and *astringent*; in large dose internally a *reflex emetic.*

1. **Zinci Sulphas.**—Zinc Sulphate. $ZnSO_4,7H_2O$.
CHARACTERS.—Colourless, prismatic crystals or powder; taste metallic, astringent. *Solubility.*—10 in 7 of water.
Dose.—*Emetic:* **Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.**

Preparation

Unguentum Zinci Oleatis.—Zinc Oleate Ointment. Zinc Oleate 50% in White Soft Paraffin.

2. **Zinci Oxidum.**—Zinc Oxide. ZnO.
CHARACTERS.—A soft, white, tasteless, insoluble powder.

Preparations

1. **Gelatinum Zinci.**—Gelatin of Zinc. Unna's Paste. Zinc Oxide 15% with Gelatin, Glycerin and Distilled Water.
2. **Pasta Zinci Oxidi Composita.**—Compound Paste of Zinc Oxide. Zinc Paste. Zinc Oxide 25% with Starch and White Soft Paraffin.
3. **Unguentum Zinci Oxidi.**—Zinc Ointment. Zinc Oxide 15% in Simple Ointment.
4. **Unguentum Zinci Oxidi Aquosum.**—Hydrous Ointment of Zinc Oxide. Zinc Oxide 15% in Hydrous Ointment.
5. **Suppositoria Hamamelidis et Zinci Oxidi.**—0·6 G (10 gr.) Zinc Oxide in each.

3. **Zinci Peroxidum.**—Zinc Peroxide. ZnO_2.
CHARACTERS.—A white or yellowish powder. containing ZnO, ZnO_2 and ZnOH.

4. **Calamina.**—Calamine. Basic Zinc Carbonate.

CHARACTERS.—A fine amorphous powder, pink from containing ferric oxide.

Preparation

Lotio Calaminæ.—Calamine 15% with Zinc Oxide, Glycerin and Water.

5. **Zinci Stearas.**—Zinc Stearate.

CHARACTERS.—A light, white, amorphous powder. Odour, faint, fatty. Insoluble in water.

ACTIONS AND USES

Externally.—Zinc Sulphate solutions are **astringents** because they precipitate the proteins in the secretions and superficial cells of raw surfaces and mucous membranes. They are also **antiseptic** because the Zinc ion is toxic to bacteria, and the salt precipitates bacterial proteins. In bleeding they are **hæmostatic** by precipitating and coagulating the blood proteins. In strong concentrations Zinc Sulphate is irritant, and **caustic** by withdrawing water from the cells, coagulating the cell proteins, and thus necrosing the tissues. Ionization with 2 per cent. Zinc Sulphate is used on the gums for pyorrhœa alveolaris and on the nasal mucosa for hay fever and persistent catarrhs.

For its astringent and antiseptic properties the Sulphate (1/2 to 1 per cent.) is frequently employed as a lotion to limit discharges from mucous surfaces and promote the healing of ulcers and wounds, especially when granulations are exuberant; and for conjunctivitis and other inflammatory conditions affecting the eye, the Sulphate in strengths of 0·25 to 0·5 per cent. (1/2 to 2 gr. per fl. oz.) is dropped into the conjunctival sac. Injections of the same strength are used for gonorrhœa and leucorrhœa. A solution of Zinc Sulphate, 2 gr., with Compound Tincture of Lavender, 12 min., in water 1 fl. oz., is the well-known "Red Lotion." Spraying the naso-pharynx with 1 per cent. Zinc Sulphate solution has been found to give some degree of protection from the virus of poliomyelitis.

The insoluble Zinc salts, Oxide, Calamine and Stearate, are all protectives, but acid-forming bacteria produce from them traces of soluble Zinc salts which act as antiseptics and mild astringents. These salts are extensively used in the form of dusting powders, often with Starch and Boric Acid, as protectives for excoriations, to allay itching and intertrigo, check excessive perspiration and absorb discharges in weeping eczemas. Pastes, Lotions, and Ointments containing them (15 to 20 per cent.) are soothing protectives for dry eczemas, acne, irritable or inflammatory skin diseases, e.g. dermatitis, prurigo, etc., and for varicose ulcers. Lotio Calaminæ with 2 per cent. of Ichthammol is a good skin sedative.

Zinc Peroxide is antiseptic to anaerobic organisms and protective; it is applied as a paste with water to ulcers, wounds and diabetic gangrene.

Internally.—Zinc Sulphate is astringent on the mucous membrane of the mouth, throat and nose, and is used in the form of mouth-washes, gargles, paints or instillations (1/2 to 1 per cent.) in the treatment of gingivitis, tonsillitis, pharyngitis, coryza and middle ear disease.

In the *stomach* Zinc Sulphate is irritant and therefore a **reflex emetic**; the action is somewhat unreliable but is usually rapid and accompanied by slight depression only.

In the *intestine* small doses of the Sulphate are astringent, but are seldom used; large doses are irritant and cause severe gastro-enteritis and collapse.

Actions after absorption.—Zinc is absorbed very slowly, and has no useful pharmacological action.

Double salts of Zinc when *injected* into frogs decrease reflex excitability, and they have been given by mouth in spasmodic conditions, but are useless.

Zinc is excreted in the intestinal tract and to some extent by the urine; it has no remote astringent effect.

Chronic Poisoning—Brass-founders' ague—is due to inhalation of finely divided Zinc Oxide or Stearate. There is at first irritation in the throat and later a "chill" with fever, muscle and joint pains, headache, and lassitude; free perspiration precedes recovery, which is usually rapid.

CUPRUM. COPPER. Cu. 63·54

The Copper ion is *astringent* and *antiseptic*; in large dose internally a *reflex emetic.*

Cupri Sulphas.—Copper Sulphate. Cupric Sulphate. "Blue Vitriol." "Bluestone." $CuSO_4, 5H_2O$.

CHARACTERS.—Blue, triclinic prisms. *Solubility.*—1 in 3·5 of cold water, solution strongly acid.

Dose.—*Astringent:* **Metric, 16 to 120 mg.; Imperial, 1/4 to 2 gr.**
Emetic: **Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.**

ACTIONS AND USES

Externally.—Copper Sulphate in solid form is a powerful **caustic** if applied to raw surfaces and mucous membranes because it precipitates the cellular proteins, and the Copper ion is also toxic; the liberation of sulphuric acid by the formation of copper albuminate causes smarting pain locally. It is applied to control warts, exuberant granulations and trachoma; the dried powdered salt is also used as an astringent, antiseptic caustic for the septic pockets in pyorrhœa alveolaris. Solutions of the salt (1/2 to 1 per cent.) are typical metallic **astringents** and **antiseptics** for raw and mucous surfaces but are now rarely used. As a wash for the conjunctiva in trachoma, 1/4 to 1/2 per cent. strengths are suitable. As a sanitary antiseptic it has been used (1 part in 2–10 million) to purify water from algæ, fungi, protozoa and the snail host of schistosoma, but it is a not good bactericide.

Internally.—Copper Sulphate in solution is seldom used as an astringent in the mouth because of its metallic taste, acidity and liability to stain the teeth green. In the *stomach*, Copper Sulphate is converted into the albuminate by the food; it irritates the gastric mucosa, so that after brief nausea, a rapid **reflex emetic** action ensues. It is suitable only for poisoning by phosphorus, upon which is formed a film of insoluble copper phosphide. A solution of 0·3 G (5 gr.) in 2 fl. oz. should be sipped every few minutes, but if this fails to cause emesis, the stomach must be emptied by a stomach-tube. In the *intestine*, small doses have an **astringent** and **antiseptic** action and were formerly used to treat bacterial diarrhœa.

Actions after absorption.—Copper is absorbed slowly from the intestine in traces which do not affect the tissues, but are excreted by the bile and urine. Recent work has suggested that minute traces of Copper—0·5 to 1 mg (1/120 to 1/60 gr.) doses of Sulphate—may have a reinforcing action in promoting the assimilation of iron salts in anæmias. Nutritional hypochromic and secondary aplastic anæmias improve more rapidly on the combined metals.

ALUMINIUM. ALUMINIUM. Al. 26·97

Aluminium salts are *antiseptics* and *astringents* and, internally, *reflex emetics.*

1. **Alumen.**—Alum. Aluminium Potassium Sulphate. $AlK(SO_4)_2$, $12H_2O$ or Aluminium Ammonium Sulphate. $AlNH_4(SO_4)_2$, $12H_2O$.

CHARACTERS.—Colourless, transparent octahedra or powder; taste, sweetish, astringent. *Solubility.*—1 in 10 of water (solution acid); freely in glycerin.

2. **Kaolinum Ponderosum.**—Heavy Kaolin. A native Aluminium Silicate, powdered and freed from gritty particles.

CHARACTERS.—A soft, whitish, insoluble powder.

If Kaolin is prescribed, Light Kaolin will be dispensed.

Preparation

Cataplasma Kaolini.—Kaolin Poultice. Heavy Kaolin 52·7% with Boric Acid, Methyl Salicylate, Oil of Peppermint and Thymol in Glycerin.

CHARACTERS.—A soft, yellowish paste.

3. **Kaolinum Leve.**—Light Kaolin.

CHARACTERS.—A light, white, insoluble powder.

Dose.—Metric, 15 to 60 G; Imperial, 1/2 to 2 oz.

ACTIONS AND USES

Externally.—Alum acts as an *astringent* and *hæmostatic* by precipitating proteins. Powdered Alum is sometimes used to check bleeding from the gums and superficial abrasions or cuts, and as a hardening agent for soft corns. Solutions of Alum (1 or 2 per cent.) are applied to check local sweating, to harden the skin and to prevent bed-sores. Light Kaolin is used as a protective dusting powder.

Cataplasma Kaolini, which resembles "Antiphlogistine," is a useful poulticing medium; it retains heat well and the rubefacient effect of the Methyl Salicylate, Thymol and Oil of Peppermint prolongs the counter-irritant action. It is employed to relieve referred pain and promote resolution of inflammation in pleurisy, pneumonia, synovitis, and in muscular rheumatism.

Internally.—Alum is used in astringent mouth washes (1 per cent.) for inflamed, ulcerated, bleeding or tender gums, and in gargles or sprays for tonsillitis, etc.; but the acidity of Alum if used often may attack the teeth. In the stomach, Alum in large dose (60 gr.) acts as an irritant **reflex emetic**, valuable in Lead poisoning because it forms Lead Sulphate. In small doses it is **astringent**, causing constipation, but is seldom used to treat diarrhœa.

Light Kaolin, given by mouth, coats the mucous membrane of the stomach and intestine, acts as a **protective** to it against irritation, reduces reflex peristalsis, and leads to remission of diarrhœa. The insoluble particles are also valuable as **adsorbents**; their large superficies renders them capable of adsorbing bacteria and bacterial toxins, and alkaloids, and thus of preventing absorption of these by the intestine. Light Kaolin, suspended in water, is therefore employed in large doses (30 to 60 G), as adjuvants in treating Asiatic cholera, acute bacillary dysentery, ulcerative colitis and persistent diarrhœa.

Aluminium Hydroxide (hydrated) is available as a Gelatum or Gel (B.P.C.), **Dose.**—4 to 8 Mils (60 to 120 min), and as Gelatum Siccum, **Dose.**—0·3 to 0·6 G (5 to 10 gr.) and as Tablets.

It is a slowly acting antacid which adsorbs H-ions and does not cause alkalosis. The viscous gel is prescribed, diluted with milk or water, in hyperchlorhydria and gastric ulcer after the two-hourly feeds; during convalescence, the dried gel may be given after meals in tablet form.

Actions after absorption.—Aluminium salts are not absorbed into the blood to any appreciable extent, and the traces dissolved from aluminium cooking utensils have no toxic significance.

FERRUM. IRON. Fe. 55·84

The Iron ion is *astringent*, *styptic* and *hæmatinic*.

A. FERROUS PREPARATIONS

1. **Ferrum.**—Iron. Annealed Iron Wire of 0·1 mm. diameter.

2. **Ferri Carbonas Saccharatus.**—Saccharated Iron Carbonate. $xFeCO_3$, $yFe(OH)_2$. Contains 50% of ferrous salts calculated as Carbonate, $FeCO_3$, mixed with Glucose.

CHARACTERS.—A greenish-brown powder; taste sweet, slightly ferruginous. 2 G (30 gr.) contain 0·5 G (7½ gr.) of Iron.
Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

3. **Ferri Sulphas.**—Ferrous Sulphate. $FeSO_4,7H_2O$.

CHARACTERS.—Green, rhombic prisms or bluish-green powder; taste astringent. *Solubility.*—1 in 1½ of water. 0·3 G (5 gr.) contains 0·06 G (1 gr.) of Iron.
Dose.—Metric, 0·2 to 0·3 G; Imperial, 3 to 5 gr.

Preparations

1. **Ferri Sulphas Exsiccatus.**—Exsiccated Ferrous Sulphate, $FeSO_4$, H_2O.

CHARACTERS.—A greyish-white powder; taste, astringent. *Solubility.*—1 in about 10 of water slowly. 0·2 G (3 gr.) contains 0·06 G. (1 gr.) of Iron.
Dose.—Metric, 60 to 200 mg.; Imperial, 1 to 3 gr.

2. **Pilula Ferri Carbonatis.**—Pill of Iron Carbonate, Blaud's Pill. Prepared from Exsiccated Ferrous Sulphate and Exsiccated Sodium Carbonate with Tragacanth, Acacia, Liquid Glucose and Water as excipients. Contains 20% of Ferrous Carbonate. 2 G (30 gr.) contains 0·2 G (3 gr.) of Iron.
Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

4. Syrupus Ferri Phosphatis Compositus.—Compound Syrup of Ferrous Phosphate. Parrish's Syrup. Chemical Food. Contains Ferrous Phosphate $Fe_3(PO_4)_2$, 0·9% and Calcium Phosphate, $Ca_3(PO_4)_2$, 1·4%, with small amounts of Potassium and Sodium Phosphate and Cochineal in 70% of Sucrose dissolved in Orange Flower Water and Distilled Water. 8 Mils (120 min.) contain 0·034 G (1/2 gr.) of Iron.

CHARACTERS.—A red fluid; taste sweet, slightly chalybeate.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.

B. FERRIC PREPARATIONS

1. Liquor Ferri Perchloridi.—Solution of Ferric Chloride. A 15% solution of Ferric Chloride, $FeCl_3$, in water.

CHARACTERS.—A yellow, acid fluid; taste sour, astringent, ferruginous. 1 Mil (15 min.) contains 0·05 G (4/5 gr.) of Iron.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

SCALE PREPARATION

2. Ferri et Ammonii Citras.—Iron and Ammonium Citrate. Made by dissolving freshly precipitated Ferric Hydroxide in a hot solution of Citric Acid, neutralizing with Ammonia, evaporating and drying in thin layers on porcelain or glass plates. 3 G (45 gr.) contains 0·6 G (9 gr.) of Iron.

CHARACTERS.—Deep-red, transparent scales, slightly deliquescent; taste sweet, ferruginous. *Solubility.*—2 in 1 of water, feebly acid.
Dose.—Metric, 1 to 3 G; Imperial, 15 to 45 gr.

Incompatibles of Preparations of Iron

Hydrates, Oxides and Carbonates give green precipitates with soluble Ferrous salts, brown with Ferric salts. Tannic Acid gives a deep blue-black with Ferric salts; and preparations of Iron therefore change to brown or black those of Gentian, Orange, Cloves, and Digitalis, but can be given in Infusion of Quassia or of Calumba.

ACTIONS AND USES

Externally.—Liquor Ferri Perchloridi has an **astringent** action on wounds and mucous surfaces but, being acid, it is also irritant. It forms with proteins a dense precipitate which redissolves as an acid-albumin if too much Liquor be applied; it is used occasionally to check exudations from ulcers. Liquor Ferri Perchloridi, by coagulating the plasma, is a **hæmostatic** for superficial wounds; it acts best if painted over a wisp of cotton-wool, but it causes smarting pain.

Internally.—The astringent action of Iron is appreciated in the *mouth* as a styptic taste. The Liquor, diluted 1 in 8, may be used as a paint for tender bleeding gums and for tonsillitis. Iron preparations, by conversion into the Sulphide, blacken the teeth; this may be avoided by drinking fluid preparations through a glass tube and by brushing the teeth frequently.

In the *stomach* Ferrous Carbonate and Pilula Ferri Carbonatis are converted partly into the Chloride; this has a mild **astringent** action because it precipitates proteins in the food and superficial cells of the mucous membrane. Ferrous Sulphate and Liquor Ferri Perchloridi are more astringent and may in consequence cause indigestion; in large doses they are irritant and may reflexly cause vomiting. They are therefore inadvisable when the gastric functions are impaired and, when prescribed, are directed to be taken well diluted after meals.

Ferri et Ammonii Citras, a scale preparation, which does not ionize in the stomach, is not astringent and therefore does not interfere with digestion; it is a suitable means of giving iron to dyspeptic and convalescent cases.

Freshly precipitated Ferric Hydroxide, given freely with water, adsorbs Arsenious Acid and is used as an **antidote** in acute poisoning from Arsenic, but the stomach must be emptied.

In the *duodenum* Iron salts are converted into the carbonate, hydroxide or albuminate; they are absorbed in the duodenum and in the upper jejunum probably in a soluble and ionized ferrous state. Unabsorbed Iron salts continue to exert their **astringent** action upon the intestinal mucous membrane and contents, and ultimately give rise to constipation. This **constipating influence** of Iron is undesirable during the treatment of anæmia and can be avoided by simultaneous administration of a purgative, e.g. Cascara or Aloes, in small dose, or by giving salines. Unabsorbed Iron is evacuated as the sulphide, which darkens the fæces.

Absorption and Excretion of Iron.—The body requires daily about 12 to 15 mg. of Iron and the average daily diet contains between 10 and 20 mg. The organic Iron in food is converted by the gastric acid into more soluble and absorbable inorganic salts. Ingested Iron becomes absorbed in some soluble, ionic, ferrous form through the columnar epithelial cells of the duodenum and, to a lesser extent, of the upper jejunum; it passes directly into the plasma (serum Iron) where it circulates probably in the ferrous state. It is thus transported to be converted into hæmoglobin for the growing corpuscle at the erythroblast–normoblast stage of its development, or to be stored as "reserve" Iron. The use of radio-active Iron (Fe^{59}) has shown that the plasma content is raised after one hour, reaches a maximum in twelve hours, and returns to normal in two days; further, radio-active Iron is found within blood corpuscles after four hours and exists wholly as hæmoglobin within a week, hence the absorbed Iron must be very rapidly utilized by the bone marrow.

In a healthy individual, however, very little of the ingested Iron is absorbed, whereas in growing children, pregnant women and in anæmia, Iron is freely absorbed. The absorbing epithelium appears to have a selective capacity depending on the amount of "reserve" Iron in the body, and it is believed that, when the intestinal mucosa becomes relatively "saturated" with Iron, it ceases to absorb more until the "reserve" Iron in the tissues, and consequently the plasma Iron, has become depleted. Iron derived from corpuscular breakdown is placed in reserve and, after hæmorrhage, the body calls first on its reserve stores for replacement of hæmoglobin; hence in a healthy person hæmoglobin recuperation after hæmorrhage is rapid; it has also been found that an increased rate of duodenal absorption of ingested Iron may not start for some days if there has been a large reserve. The "reserve" Iron is stored chiefly in the liver and spleen, particularly by the Kupffer cells and splenocytes, in the bone marrow and, to a small extent, in the kidney. Surplus "reserve" Iron is excreted in small daily amounts (0·1 to 0·25 mg.) by the kidney, and little, if any, of the normal Iron of the body is excreted through the intestine.

From estimations of the serum or plasma Iron in Iron-deficiency anæmia, it has been found that **ferrous salts are more rapidly absorbed** than ferric, and that the amount of **absorption is** in fairly direct **proportion to the dose,** hence large doses—but short of those causing gastric upset—are more rapidly effective in treatment. In Iron-deficiency anæmias, hæmoglobin is reconstituted in amounts requiring about 20 to 50 mg. of Iron daily, which is another reason for the administration of massive dosage.

Actions after Absorption.—Iron salts increase the amount of hæmoglobin and the numbers of red corpuscles if they are deficient, but will not increase them above their normal amounts. An insufficient intake of Iron is unusual but may arise in undernourished women and in children fed on milk and cereals. Iron-deficiency anæmia is of the microcytic hypochromic type and responds to administration of Iron salts or to correction of the diet. It should be remembered that, although a dose of an Iron salt raises the serum Iron percentage after half an hour to a peak in 3 to 5 hours, the synthesis of hæmoglobin is slow, therefore treatment extending over six to ten weeks has to be anticipated.

The dosage of Iron salts, for the reasons given above, must be adequate. It should provide for absorption by the intestine, daily amounts of the soluble ferrous salts containing at least 0·1 G (1½ gr.) Iron, and of less soluble salts, e.g. Pil. Ferri Carb., five or more times these amounts. Large daily doses are now given of Ferrous Sulphate, 15 gr. (3 gr. Fe), Pil. Ferri Carb., 90 gr. (9 gr. Fe), and, as ferric salts are probably reduced to ferrous before absorption, Ferri et Ammonii Citras, 90 gr. (16 gr. Fe). Such large doses are effective **hæmatinics** in microcytic hypochromic (secondary) anæmias arising from accidental and post-partum hæmorrhage, menorrhagia, syphilis and malaria, as well as during convalescence from infectious fevers, endocarditis, and nephritis, and also in the treatment of splenic anæmia. During the recovery from Iron deficiency anæmias, it is important to advise a diet rich in Iron, e.g. beef, liver and legumens.

In **chlorosis** and the **amenorrhæa** of adolescent women, the administration of Iron salts is peculiarly effective. It is useful also in the **achlorhydric anæmia** of middle-aged women; and, in the **nutritional anæmias** of children, either Ferri et Ammonii Citras or a ferrous preparation is of value and may advantageously be accompanied by liver therapy. In pernicious anæmia Iron salts are given only if the diet be deficient in Iron.

The so-called **"tonic" action** of Iron is entirely a result of the improved condition of the blood. With recovery from the anæmia and consequent improvement in the oxygen supply to the tissues, the concomitant symptoms of cardiac weakness, dyspnœa, cyanosis, lassitude, and muscular weakness rapidly disappear, while the digestive functions and appetite also recover.

Copper and Manganese as Synergists of Iron.—It has been found experimentally that traces of Copper—0·5 to 1 mg. (1/120 to 1/60 gr.)—enhance the advantageous effects of Iron in anæmia. The same action has been attributed on clinical evidence to Manganese and Arsenic, but the effects are so far unexplained and, by many clinicians, doubted.

Uses of Different Preparations of Iron.—The choice of a preparation of Iron for administration in anæmia is determined essentially by the condition of the digestive organs. In cases where dyspepsia is a prominent symptom the least irritant and astringent ferrous preparations should be selected, namely Ferri Carbonas Saccharatus as a powder, or Pilula Ferri Carbonatis. The scale (ferric) preparation is also devoid of astringent action, therefore Ferri et Ammonii Citras is particularly suitable.

Of the astringent preparations, Ferrous Sulphate is best given well diluted in mixture form; and Syrupus Ferri Phosphatis Compositus is a hæmatinic acceptable by children during convalescence.

Iron is a constituent of many natural mineral waters, the most important chalybeate springs being those of Flitwick, Harrogate, and Trefriw in Britain; and Spa, Schwalbach, Levico, Roncegno, and St. Moritz on the Continent. The amounts of Iron they contain are small, but the regimen enjoined of appropriate periods of rest and open-air exercise or recreation contributes to their success and popular appraisement.

Intravenous Injection of Iron.—Intravenous Iron therapy has become successful by the use of Saccharated Iron Oxide of which each 100 mg. Iron dose will raise the hæmoglobin by about 4 per cent., thus it is practicable to estimate the dosage required to correct the hæmoglobin deficiency. **Ferrivenin** is a 2 per cent. stable solution of Saccharated Iron Oxide supplied in 5-Mil ampoules containing 100 mg. Iron for intravenous administration. After smaller initial test doses, 5 Mils are injected daily, or on alternate days, up to the required amount; mild reactions of headache and malaise occasionally occur. From the time of starting injections, the rise in the reticulocytes, hæmoglobin and erythrocytes begins about the second week, the reticulocyte peak being in the third week and then falling rapidly back to normal. The full recovery of hæmoglobin and erythrocytes is reached about the sixth or eighth week. Ferrivenin may also be given by intravenous drip in amounts representing 1 G Iron, diluted about 1 in 20 with 5 per cent. Dextrose solution.

MANGANESIUM. MANGANESE. Mn. 54·93

Potassium Permanganate is essentially an *antiseptic.*

Potassii Permanganas.—Potassium Permanganate. $KMnO_4$.

CHARACTERS.—Dark-purple, iridescent prisms; inodorous; taste sweet, astringent. *Solubility.*—1 in 20 of water, solution purple and neutral. *Incompatible* with oxidizable substances.

Dose.—Metric, 60 to 200 mg.; Imperial, 1 to 3 gr.

ACTIONS AND USES

Externally.—Potassium Permanganate is an irritant and **caustic** in the solid state. In solution it gives up oxygen which oxidizes the proteins in organic matter; it is thus a powerful **disinfectant**, destroying toxins and bacteria; it also acts as a **deodorant**. In weaker strengths it is antiseptic, inhibiting the growth of bacteria. Since it is rapidly reduced by organic matter, solutions soon lose their activity; this is indicated by a change in colour to brown. As a disinfectant (1: 100 to 1: 500), it is employed to disinfect stools and septic discharges, soiled utensils and water-closets; and as an antiseptic for fœtid perspiration and ulcers (1: 1,000), as enemas in colitis or injections in gonorrhœa (1: 3,000, and as douches in vaginitis, ozæna and uterine cancer (1: 5,000). Permanganate is an **antidote to snake-bite**: the bite is incised deeply and cauterized with the crystals, or an immediate local injection is made of a 1 per cent. solution.

Internally.—Potassium Permanganate is employed as a deodorant mouth-wash (1: 5,000), and as a gargle in sore throat. Since it oxidizes Morphine and Phosphorus, it is used (1: 2,000) to wash out the stomach in poisoning by these drugs.

Actions after Absorption.—Potassium Permanganate was formerly given as a **hæmatinic** and it has been suggested that Manganese acts as a synergist in promoting absorption of Iron.

HYDRARGYRUM. MERCURY. Hg. 200·61

Mercury is an *antiseptic* and *astringent* externally, *purgative* internally and a *specific* against the parasites of syphilis and certain other diseases.

1. **Hydrargyrum.**—Mercury. Hg.

CHARACTERS.—A silver-white, heavy liquid with metallic lustre; easily divisible into globules.

Preparations

1. **Hydrargyrum cum Creta.**—Mercury with Chalk. "Grey Powder." 33% with Chalk, which disperses the Hg into fine particles.
Dose.—Metric 60 to 300 mg.; Imperial, 1 to 5 gr.

2. **Tabellæ Hydrargyri cum Creta.**—60 mg. (1 gr.) in each.

3. **Pilula Hydrargyri.**—Mercury Pill. "Blue Pill." 33% with Syrup, Liquid Glucose, Glycerin and Liquorice.
Dose.—Metric, 0·25 to 0·5 G; Imperial, 4 to 8 gr.

4. **Unguentum Hydrargyri.**—Mercury Ointment. Blue Ointment. 30% Hg with Oleated Mercury 1·5%, Wool Fat, White Beeswax and White Soft Paraffin.

5. **Unguentum Hydrargyri Dilutum.**—10% Hg in Simple Ointment. *If Blue or Mercury Ointment is prescribed, the Dilute Ointment will be dispensed.*

6. **Unguentum Hydrargyri Compositum.**—Compound Mercury Ointment. "Scott's Dressing." Mercury Ointment 40% with Yellow Beeswax, Olive Oil and Camphor. Contains 12% Hg.

7. **Unguentum Hydrargyri Nitratis Forte.**—Mercuric Nitrate Ointment. Made by dissolving Mercury 10 in Nitric Acid 30 and incorporating with Lard and Olive Oil to 100.

8. **Unguentum Hydrargyri Nitratis Dilutum.**—Diluted Mercuric Nitrate Ointment. 20% of Strong Ointment in Yellow Soft Paraffin.

2. **Hydrargyri Oxidum Flavum.**—Yellow Mercuric Oxide. HgO.

CHARACTERS.—A yellow, amorphous, insoluble powder.

Preparations

1. **Oculentum Hydrargyri Oxidi.**—Yellow Mercuric Oxide 1% in the Wool Fat and Soft Paraffin basis for Oculenta.

2. **Oculentum Atropinæ cum Hydrargyri Oxido.**—1% with 0·125% Atropine Sulphate in the basis for Oculenta.

3. **Hydrargyri Perchloridum.**—Mercuric Chloride. Corrosive Sublimate. $HgCl_2$.

CHARACTERS.—Heavy, colourless, crystalline masses or powder; taste, acrid, metallic. *Solubility.*—1 in 18 of water.

Dose.—Metric, 2 to 4 mg.; Imperial, 1/32 to 1/16 gr.

Preparation

Liquor Hydrargyri Perchloridi.—1 dissolved in 1,000 of Distilled Water. Strength 0·1% (1/16 gr. in 60 min.).

Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

4. **Hydrargyri Oxycyanidum.**—Mercuric Oxycyanide. $HgO, 3Hg(CN)_2$.

CHARACTERS.—A white crystalline powder. *Solubility.*—Almost completely 1 in 18 of water, alkaline.

5. **Phenylhydrargyri Nitras.**—Basic Phenylmercuric Nitrate. $C_6H_5HgOH, C_6H_5HgNO_3$.

CHARACTERS.—White plates, or crystalline powder, slightly soluble in water.

6. **Hydrargyri Subchloridum.**—Mercurous Chloride. Calomel. HgCl.

CHARACTERS.—A dull-white, heavy, nearly tasteless powder. *Solubility.*—Insoluble in water; volatilized by heat.

Dose.—Metric, 30 to 200 mg.; Imperial, 1/2 to 3 gr.

Preparations

1. **Tabellæ Hydrargyri Subchloridi.**—60 mg. (1 gr.) in each.

2. **Unguentum Hydrargyri Subchloridi.**—Calomel Ointment. 20% in Simple Ointment.

7. **Hydrargyrum Ammoniatum.**—Ammoniated Mercury. "White Precipitate." NH_2HgCl.

CHARACTERS.—A white, heavy, tasteless, insoluble powder.

Preparation

Unguentum Hydrargyri Ammoniati.—Ammoniated Mercury Ointment. "White Precipitate Ointment." 2·5% with Simple Ointment.

irritation of the mucosa, vomiting, gastric inflammation, and, by their toxicity, necrosis. The insoluble mercurials do not influence the stomach.

In the intestine Mercury salts are purgative, but the soluble salts cannot be used because they are too irritant and toxic to the mucosa and are rapidly absorbed. The insoluble preparations—*Blue Pill*, Grey Powder or Calomel—slowly form oxides in the alkaline duodenum and small amounts are dissolved, probably as albuminates which irritate the intestinal mucous membrane and reflexly increase peristalsis. The increased movements occur chiefly in the small, but also in the large, intestine, so that the contents are transmitted more rapidly and less water is, therefore, absorbed from them. The irritation is mild in character and griping contractions are unusual; a soft or loose stool, often of a green colour, is evacuated in about 8–10 hours, and is commonly repeated as some of the insoluble Mercurial remains in the bowel. The green colour is due either to undecomposed biliverdin or to traces of Mercuric Sulphide. Calomel does not increase biliary secretion but may, by duodenal irritation, cause evacuation of the gall-bladder. A slight antiseptic action of the Mercurials, exerted by small doses of either the soluble or insoluble salts, in the intestine has been proved by the decrease in the ethereal sulphates in the urine; but the less absorbable Sulphonamides are more effective.

Calomel is useful as a purgative to clear the intestine. It may be prescribed conveniently in tablets, pills or powders, either as a single dose at night or in divided doses of 0·03 G (½ gr.) at intervals of half to one hour until 0·15 G (2½ gr.) have been given; the latter method ensures more even distribution of the drug. Salines are often advised on the following morning to remove residual Calomel. Mercurial purgatives are unsuitable for chronic constipation as part of the Mercury is absorbed. Pilula Hydrargyri may be used instead of Calomel; for children, Hydrargyrum cum Creta is a very effective means of treating diarrhœa with offensive stools containing undigested food, and of clearing the bowel during febrile illness. Mercury is well borne by children and, in appropriate small dosage, Liquor Hydrargyri Perchloridi is sometimes used in treating bacillary diarrhœa in infants.

Absorption of Mercury from the Intestine.—Both soluble and insoluble Mercury salts are absorbed from the intestine in the form of proteinates; the soluble salts are absorbed rapidly and completely, the insoluble more slowly and to a much smaller extent. The absorbed metal circulates as a soluble proteinate and is stored in the tissues, chiefly in the liver, spleen, kidneys and intestine, but it penetrates into all tissues. Excretion of the metal occurs through most mucous membranes but chiefly through the large intestine and the kidney. Some excretion also occurs through the placenta into the fœtus and prenatal treatment with Mercury was formerly used in syphilis.

Actions after absorption.—Acute symptoms. A poisonous dose, e.g. 1 G, of the soluble Perchloride quickly causes a severe gastroenteritis with swelling and necrosis of the mucous membrane in the mouth, pharynx and stomach; vomiting follows of material showing shreds of mucous membrane and blood; death may occur quickly from shock and circulatory collapse. In less acute cases the primary symptoms may subside and, after a day, stomatitis, enteritis and colitis develop with rice-water stools containing blood; acute tubular or sometimes glomerular nephritis, with albumin and casts, precedes a decrease in urinary secretion or suppression of urine.

Chronic poisoning (mercurialism or hydrargyrism) results from continued dosage with the metal, which accumulates in the tissues, but the symptoms are due mainly to the irritant action of the Mercury during its excretion. The earliest to appear is a metallic taste in the mouth with fœtid breath, followed by salivation, swelling of the gums (stomatitis), dyspepsia and diarrhœa, all due to the irritation of the Mercury upon the glands and mucous membrane of the alimentary tract during its excretion. Later, from toxic action on the cells and bacterial infection of the weakened mucosa, ulcers appear on the gums and fauces, the teeth become loose and necrosis of the jaw may occur. The enteritis often progresses to ulceration, particularly in the large intestine, where the chief excretion takes place, and ulcers are more likely to occur when dosage by mouth contributes to the toxic effect of the excreted Mercury. Excretion through the kidney causes, by irritation, at first diuresis, but this is followed by albuminuria and, in slow poisoning, by tubular and interstitial nephritis. In advanced cases the prolonged enteritis leads to anæmia, emaciation and general cachexia with weak rapid pulse and dyspnœa. Skin eruptions of an erythematous or eczematous type may appear. Peripheral neuritis is a common sequel; it may show itself at an early stage in the form of muscular weakness and tremors, the latter seen often in the tongue and lips (Mercurial tremors), and shooting pains in the limbs may also occur. In children the permanent teeth exhibit horizontal ridges (Mercurial teeth of Hutchinson) caused by interference with calcification.

Mercury Salts in the Treatment of Syphilis.—About A.D. 1500, syphilis was recognized as a distinct disease; Mercury was first employed about A.D. 1000 by the Arabian physicians to treat skin diseases. Until 1910, it was the only specific remedy for syphilis. In the modern treatment of syphilis, Mercury is recognized to be much less effective alone than in combination with the Organic Arsenicals, and on account of their lower toxicity Bismuth preparations have now superceded those of Mercury. The methods of administering Mercury in syphilis are now rarely employed:

(1) *Inunction*, daily of 4 G (60 gr.) of Unguentum Hydrargyri into different thin areas of skin was used when oral or intramuscular administration was not tolerated. (2) *Oral administration* of Liquor Hydrargyri Perchloridi, or pills containing 0·06 G (1 gr.) of Calomel thrice daily, the evening pill containing 0·06 G (1 gr.) of Opium Pulveratum to reduce purgation. (3) *Intramuscular Injection* into the gluteal muscles of oily suspensions of Mercury (Grey Oil) or Calomel (Calomel Cream), containing 0·06 G (1 gr.) of Mercury and given at weekly intervals for 10 weeks, was the routine method along with intravenous Neoarsphenamine. (4) *Intravenous Injection* of Oxycyanide of Mercury, 0·01 G (1/6 gr.), dissolved in 5 Mils of Normal Saline Solution gave a rapid, but brief, high blood concentration but had no advantage in treating syphilis.

Action of Mercury in Syphilis.—Although soluble Mercury preparations are toxic to the Treponema pallidum *in vitro*, the maximal concentration in the blood, about 1: 1,000,000, seems inadequate to have this effect. Mercurial treatment successfully, but only slowly, clears up the primary lesions and reduces the number of spirochætes; if persisted with, it prevents, or renders less severe, the secondary stage. Secondary cutaneous eruptions and mucous lesions disappear under its influence; and tertiary manifestations also respond to mercurial treatment, but, in the tertiary stage, the drug is best combined with Iodides which aid resolution of gummata. Under Mercury treatment alone relapses are frequent, and its essential value is to maintain an adequate amount of an antisyphilitic remedy in the tissues during the intervals between the injections of the more effective antisyphilitics. Mercurial treatment has now been displaced by the much less toxic Bismuth therapy.

It may be used along with Potassium Iodide with successful results in cardiovascular and visceral syphilis, when Arsenical injections are contra-indicated.

Diuretic Action of Mercury Preparations.—Mercury salts during excretion by the kidney retard the reabsorption of fluid from the renal tubules and thus small doses of Mercury salts are effective **diuretics.** Calomel in doses of 0·02 to 0·06 G (1 to 3 gr.) was formerly used as a diuretic in cardiac œdema and is occasionally prescribed in such cases while under Digitalis therapy. (Guy's Pill is Digitalis 1, Squill 1, Mercury Pill 1.) Within recent years organic Mercury compounds, e.g. Mersalyl, have been used by injection as diuretics because of the diarrhœa induced by Calomel and the uncertain rate of its absorption.

Mersalylum.—Mersalyl. "Salyrgan." "Mercurgan." The Sodium salt of Salicyl-(γ-hydroxymercuri-β-methoxypropyl)-amide-O-acetic acid. $(HgOH)CH_2 . CH(OCH_3)CH_2 . NHCO . C_6H_4 . O . CH_2 . COONa$.

CHARACTERS.—A white, odourless, deliquescent powder; taste bitter; containing 40% of Hg. *Solubility.*—1 in 1 of water: Solutions of it, containing NaCl, may form toxic Hg compounds unless Theophylline is present as a buffer.

Preparation

Injectio Mersalyli.—Injection of Mersalyl. Mersalyl 10% with Theophylline 5% and Sodium Hydroxide to *p*H 7·8 in Water for Injection. 2 Mils (30 min.) contain 0·2 G (3 gr.) Mersalyl.

Dose.—*By intramuscular or intravenous injection:*

Metric, 0·5 to 2 Mils; Imperial, 8 to 30 min.

ACTIONS AND USES

Mersalyl acts as a **powerful diuretic by retarding tubular reabsorption** by the kidney; the Theophylline, which prevents ionic dissociation of Mersalyl in presence of salts, also augments the diuresis by increasing glomerular filtration. Mersalyl Injection is commonly given intramuscularly deep into the gluteal region; as it is irritant, it must not be given subcutaneously. It may also be injected intravenously, the Injection being first diluted with 10 or 20 Mils of sterile Saline Solution and given slowly. Initially, the smaller dose of 0·5 Mil (8 min.) is used and this is increased up to 2 Mils (30 min.) at intervals of 2, 3 or 5 days as the œdemic condition requires. The action begins in one or two hours, is maximal in about eight hours, and passes off during the following day. The diuretic effect is often dramatic and 90 to 100 fl. oz. of urine may be passed within the day, so that the œdema is greatly reduced, and therewith venous and intraspinal pressures are lowered, while cyanosis and other accompanying symptoms are relieved. It is best given early in the morning so that its action is declining by the evening. The diuresis is enhanced by giving Ammonium Chloride for several days prior to the Injection (*see* p. 52). Suppositories of Mersalyl 0·4 G (6 gr.) with Theophylline 0·2 G (3 gr.) may be inserted once a week to maintain the diuretic effect, but they often produce rectal irritation. Mersalyl 0·06 G (1 gr.), taken by mouth, is much less effective and is liable to irritate the stomach.

Mersalyl is most effective in relieving œdema due to congestive cardiac failure, but is also valuable in hepatic œdema and that of chronic parenchymatous nephritis. Mersalyl can be a renal irritant and is contra-indicated in acute nephritis; and should be avoided in enteritis because its excretion by the bowel may cause diarrhœa.

Novurit. Mercurin.—A complex organic mercurial compound. *Dose.*—0·5 to 2 Mils of a 10% solution intravenously; also effective as a diuretic when used in the form of suppositories containing 0·5 G.

Precautions in the use of Mercurials.—(1) Idiosyncrasy to Mercury is not uncommon and hydrargyrism may occur from small doses. (2) Salivation may be postponed by regular oral hygiene and the use of a mouth-wash containing Potassium Chlorate or Hydrogen Peroxide. If salivation occurs the use of Mercury should be interrupted. Severe poisoning should be treated by injections of Dimercaprol (*see* p. 383). (3) Mercurial treatment is contra-indicated in renal disease and in anæmic and debilitated subjects.

Mercurochromum (B.P.C.).—Mercurochrome "220." Sodium dibromohydroxymercury fluorescein. $C_{20}H_7O_5Br_2HgOHNa_2$.

CHARACTERS.—Iridescent green scales, forming a red solution in water.

Actions and Uses.—Mercurochrome is an *antiseptic* which in solution ionizes only slightly, is almost non-irritant, has a low cellular toxicity and does not penetrate living tissues. Its bacteriostatic power in 1 or 2% solutions is only moderate although increased in slightly acid media. It is occasionally used as a surface antiseptic on the skin to prevent spreading of boils and to treat ringworm or other mycotic skin diseases.

PHOSPHORUS. PHOSPHORUS. P. 30·98

Preparations of yellow **Phosphorus** used to be prescribed as nervine tonics in debility, convalescence and neurasthenia. They have no influence on nervous tissue and have rightly fallen into desuetude. **Calcium and Sodium Hypophosphites** are still frequently given as restoratives in general and nervous debility but there is no direct evidence of their value. Various **Glycerophosphates** were introduced for the same purpose because of their chemical relationship to Lecithin, which has also been employed. It is improbable that these preparations have any therapeutic value.

Phosphorus was formerly used in the treatment of rickets, but the cause of rickets is rarely lack of phosphates in the diet but commonly a defective assimilation and utilization of calcium and phosphorus associated with lack of Vitamin D in the diet.

Radio-phosphorus.—The radio-active phosphorus isotope, P^{32}, is used as Disodium Hydrogen Phosphate in isotonic solution (15 mg. per Mil) with an initial activity of 0·2 to 0·4 millicurie per Mil. P^{32} penetrates all tissues but is specially taken up by rapidly growing and leukæmic cells. Intravenous injections (0·1 to 0·5 millicurie) two or three times weekly are better than oral doses, which are not wholly absorbed. The effect of the beta rays develops slowly.

In polycythæmia vera, an initial course of from 3 to 5 millicuries reduces the erythrocytes after an interval of one or two months and the remission may last two years. In chronic myeloid leukæmia, the numbers of myelocytes and myeloblasts decrease, the anæmia and splenic enlargement are reduced and the improvement may last for a year. Lymphatic leukæmia may improve but not monocytic leukæmia.

ARSENIUM. ARSENIC. As. 74·91

The trivalent Arsenic ion is highly toxic to protozoal organisms.

Arseni Trioxidum.—Arsenious Acid. White Arsenic. As_2O_3.

CHARACTERS.—A heavy white powder; or stratified, opaque, porcelain-like masses. *Solubility.*—1 in 65 of water, giving an odourless, tasteless, faintly acid solution.

Dose.—Metric, 1 to 5 mg.; Imperial, 1/60 to 1/12 gr.

Preparation

Liquor Arsenicalis.—Arsenical Solution. Fowler's Solution. Contains Potassium Arsenite. Strength 1% of As_2O_3. 0·5 Mil (8 min.) contains 5 mg. (1/12 gr.) As_2O_3.

CHARACTERS.—A colourless and odourless liquid; taste saline.

Dose.—Metric, 0·12 to 0·5 Mil; Imperial, 2 to 8 min.

ACTION AND USES

Arsenical preparations owe their actions to dissociation of the toxic trivalent ion As_2O_3. Compounds containing the pentavalent ion dissociate slowly and are therefore much less toxic, but their slow decomposition by the tissues results in the formation of trivalent compounds in strengths sufficient to be toxic to protozoal parasites.

Externally.—Arsenious Oxide is a **cellular poison.** It has no effect on unbroken skin from which little is absorbed, but if placed on a mucous membrane or raw surface, it penetrates the underlying cells and by its toxic action causes their necrosis. At first it causes pain by irritation of the sensory endings; then the drug, as it penetrates, causes progressively necrosis of nerve fibrils, lymph channels and, after initial capillary dilatation, thrombosis of the blood-vessels, so that toxic absorption or bleeding from its action is rare; for these reasons, Arsenious Oxide was used as a **caustic** in dentistry to devitalize the pulp in permanent teeth.

A 2 per cent. solution of Neoarsphenamine is a useful mouthwash in spirillar infections, chronic ulcerations of the buccal mucous membrane and Vincent's angina.

Internally.—In the stomach, small doses of Arsenious Oxide, by slight irritation of the mucous membrane, produce a feeling of warmth and stimulate appetite; they neither precipitate proteins nor delay enzyme action. Small doses of the Liquor were formerly prescribed to improve the digestive functions in convalescence. Full doses, by irritation, may cause abdominal pain and vomiting followed by diarrhœa.

Actions after absorption.—In therapeutic doses, Arsenic is readily absorbed from the intestine. Liquor Arsenicalis has acquired a reputation as a "general tonic," in debility and convalescence probably because it improves appetite, and reduces oxidative metabolism. There is clinical evidence of increased weight and bodily vigour, and greater deposition of subcutaneous fat. Small doses of Arsenic increase the resistance of erythrocytes to hæmolysis; this may account for their adjuvant effect with Iron in microcytic anæmias.

Large or repeated doses of Arsenic injure the bone-marrow, which becomes hyperæmic, the fat cells atrophy and increased numbers of erythroblasts, but fewer leucoblasts, enter the circulation. Liquor Arsenicalis is given in chronic myeloid leucæmia, but the improvement which follows is only temporary. Arsenic stimulates the osteoblasts so that in young animals it increases the formation of compact bone in the epiphyses.

In medicinal dosage Arsenic has no important effects on circulation or respiration.

Preparations of Arsenic **accelerate the proliferation of epithelium**; they improve the nutrition of the skin, increase the subcutaneous fat and render the complexion clearer. Large doses cause exfoliative dermatitis, especially on the palms and soles, pigmentation of the skin (arsenical melanosis) and keratosis. Arsenic is most useful in the treatment of subacute and **chronic skin diseases**, less so in acute cases. It is given internally in cases of psoriasis, lichen planus, pemphigus, hydroa and bullous conditions; suitable local treatment of the lesions is also necessary.

Toxic Effects of Arsenic. **Acute poisoning.**—This will arise from amounts of from 0·05 to 0·3 G of Arsenic Trioxide. The early symptoms, which may be delayed for some hours, are vomiting, dryness of the mouth and throat, thirst and difficulty of swallowing, followed by severe griping and diarrhœa, and are due to acute œdema of the mucous membranes. Vascular dilatation in the splanchnic area produces a rapid fall in blood-pressure with consequent vertigo, syncope, cyanosis and cold extremities. Death follows from exhaustion, due to the acute gastro-intestinal catarrh, in from one to three days.

Chronic Poisoning.—Repeated small doses of Arsenic produce similar symptoms. Patients complain first of dyspepsia, sickness, abdominal pains and diarrhœa. A specific action of Arsenic is to paralyse the muscle of the intestinal arterioles and to **increase the capillary permeability**; there results a vascular dilatation, blood stasis and an œdema of the intestinal mucous membrane, which appears red and swollen. The epithelial cells undergo fatty degeneration and, owing to the transudation of fluid beneath them, they become detached and leave eroded areas, while the shreds of mucous membrane and lymph form part of the "rice-water" stools which are common in chronic poisoning from Arsenic.

Absorption of the Arsenic leads to **metabolic disturbances** and to **fatty degeneration** in internal organs, the underlying cause being probably a reduction of oxidative processes. Capillary dilatation causes the reddening of, and watery secretions from, such mucous membranes as those of the conjunctiva, nose and mouth, which effects are often helpful in diagnosing the condition.

The metabolic disturbances are characterized by **accelerated katabolism** in association **with deficient oxidation**; (1) Carbohydrate metabolism is stimulated so that the glycogen in the liver decreases but, from inefficient oxidation, the intermediate product—lactic acid—appears in the blood and produces a tendency to acidosis. (2) Protein metabolism is augmented—partly from the lactic acid formation—but is also imperfect, hence leucin and tyrosin may be found in the urine. There is an increase in the excretion of urea and salts of ammonia which is formed from urea by the renal tubules to protect the alkali reserve. (3) The liver and other tissues—kidney, heart, intestinal and pulmonary epithelium—derive supplies of fat through the blood from the subcutaneous tissues but, being unable to desaturate the fat, the cells undergo fatty infiltration and degeneration. The liver enlarges, the bile-ducts are compressed and, in consequence **jaundice** develops.

Scaly desquamation (exfoliative dermatitis) of the epidermis is a common symptom in prolonged cases, or the skin may be pigmented (arsenical bronzing or melanosis). From a direct action on the nerves, **peripheral neuritis**, exhibited by areas of anæsthesia, muscular paralysis and atrophy, or partial blindness, is a late sequel in arsenical poisoning.

Tolerance to Arsenic.—A small degree of tolerance exists amongst Styrian peasants: the men believe it improves their staying powers and women take it to improve their complexion. It is not a true tolerance because the insoluble Arsenic is taken while fasting and no water is drunk for some hours afterwards.

Excretion of Arsenic.—The excretion of Arsenic is slow and incomplete; therefore it is a **cumulative poison**. After a single dose excretion commences in about four to eight hours and may continue for about ten days, because **storage** occurs in most tissues but chiefly in the liver, kidneys and bones. The elimination occurs mainly into the fæces and urine but traces can be found in the epidermis, sweat, milk, nails, and hair. Arsenic is also excreted through the placenta into the fœtus.

Precautions in administering Arsenic.—Small doses should be given at first and gradually increased lest idiosyncrasy be exhibited; they should be given after meals so as to minimize the effects on the gastro-intestinal mucous membrane. Elderly persons do not tolerate Arsenic well.

ORGANIC ARSENICAL COMPOUNDS

1. **Neoarsphenamina.**—Neosalvarsan. Neokharsivan. Novarsenobenzene. Sodium-diamino-dihydroxyarsenobenzene methylene sulphoxylate. "914."

CHARACTERS.—A yellow powder, sealed in glass phials from which air has been exhausted or replaced by an inert gas. Contains 20%

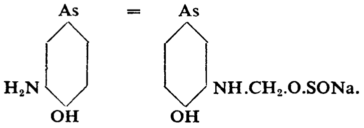
Arsenic. Store below 15° C. (60° F.); if colour has darkened, it should not be used. *Solubility.*—Easily in water; solution neutral or slightly alkaline.

Dose.—*By intravenous injection:*

Metric, 0·15 to 0·6 G; Imperial, 2½ to 10 gr.

Preparation

Injectio Neoarsphenaminæ.—The desired dose from a sealed glass phial dissolved in the required amount of Water for Injection immediately before use. As the solution decomposes rapidly with increased toxicity, its intravenous injection should be within five minutes of preparation.



Sulpharsphenamina.—Sulpharsenol. Kharsulphan. Sulpharseno-nzene. Disodium-diamino-dihydroxy-arseno-benzene dimethylene ulphite.

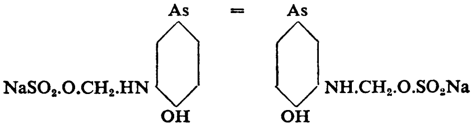
CHARACTERS.—A yellow powder, sealed in glass phials from which air has been exhausted or replaced by an inert gas. Contains 20% Arsenic. Store below 15° C. (60° F.); if colour has darkened, it should not be used. *Solubility.*—Easily in water.

Dose.—*By subcutaneous or intramuscular injection:*

Metric, 0·1 to 0·6 G; Imperial, 1½ to 10 gr.

Preparation

Injectio Sulpharsphenaminæ.—The desired dose from a sealed glass phial dissolved in the required amount of Water for Injection immediately before use. As the solution decomposes rapidly with increased toxicity, its subcutaneous or intramuscular injection should be within five minutes of preparation.



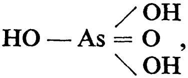
3. **Oxophenarsine Hydrochloride** (B.P.C.).—Mapharside. Mapharsen. The hemi-alcoholate of the hydrochloride of 3-amino-4-hydroxyphenylarsine oxide. C_6H_3. As: O. NH_2. OH., HCl, $\frac{1}{2}C_2H_5OH$.

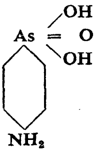
CHARACTERS.—A white, amorphous, deliquescent powder, containing 29% Arsenic, very soluble in water.

Dose.—*By intravenous injection* in 10 Mils of Water for Injection.

Metric, 30 to 90 mg.; Imperial, ½ to 1½ gr.

ARSENICAL TREATMENT OF PARASITIC DISEASES

Historical.—Arsenious Oxide, although an efficient protozoal poison in dilutions of about 1: 3,000,000, is too toxic towards man for effective use as an agent to eradicate protozoal parasites from the tissues. Ehrlich and others, therefore, searched for an organic arsenical compound which would be highly toxic to parasites (parasitotropic) and feebly toxic to higher mammalia (organotropic), i.e. one having a high "chemotherapeutic index." From the examination of many such compounds, it was found that, although the pentavalent series of the type of Arsenic Oxide,  $HO-As(=O)(OH)_2$, e.g. Atoxyl, Arsacetin, were slowly toxic to protozoa in the body, they also produced delayed poisoning in the host and their chemotherapeutic index was not high. Compounds possessing a double benzene ring linked by two trivalent Arsenic atoms were, however, found to be much more toxic to protozoal parasites than they were to the host. Ehrlich's original endeavour was to obtain a compound which in a single dose would eradicate from the body the Treponema pallidum of syphilis and possibly also the trypanosome of sleeping sickness without injury to man.



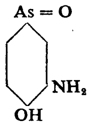
Atoxyl.

One of the earliest effective compounds was Sodium-aminophenyl arsonate or Atoxyl. This pentavalent arsenical proved capable of clearing the trypanosomes of sleeping sickness from the blood and lymphatic glands after two doses, but continued dosage with this drug, or its relative, Sodium-acetyl-amino arsonate (Arsacetin), was liable to produce permanent blindness.

The discovery of Salvarsan or Diamino-dihydroxy arsenobenzene—the 606th compound examined by Ehrlich and Hata—caused a revolution in the treatment of syphilis, and it seemed at first as if Ehrlich's "therapia sterilisans magna" had been achieved, but experience proved that, although a single dose produced a dramatic improvement in the syphilitic lesions, it was not permanetly curative. Salvarsan is an acid hydrochloride; given intramuscularly it caused great pain and, for intravenous administration (Dose, 0·4 to 0·6 G), it had to be converted by sodium hydroxide into the less soluble mono- and di-Sodium salts; this entailed careful technique and the slow injection of from 150 to 200 c.c. of solution.

A more satisfactory preparation was Neosalvarsan or Neoarsphenamine—the 914th compound—which is readily soluble in water with neutral reaction and requires no special treatment prior to injection.

Action of Organic Arsenicals on Protozoa.—The trivalent arsenicals, e.g. Neoarsphenamine, are toxic to spirochætes in concentration of about 1: 2,500 *in vitro*, but if they are first incubated with liver pulp, or given time to undergo oxidation, they become toxic in dilutions of above 1: 1,000,000. Neoarsphenamine circulates in the blood as a colloid; it becomes adsorbed probably both on the parasites and on the tissue cells, which slowly oxidize it into a trivalent arsenious oxide in amounts sufficient to be toxic to spirochætes but insufficient usually to be harmful to man. This slow formation of the toxic substances explains why, when given intravenously, two or three hours elapse before Neoarsphenamine develops a toxic action on the parasites in the lesions. It is probable that **the toxic agent** is amino-oxyphenyl arsenious oxide and that it acts by an affinity for the sulphydril group in glutathione; this theory receives support from the antidotal action of Dimercaprol and Thiosulphates (*see* p. 115) in poisoning by Organic Arsenicals.



Method and Routine of Administration.—Neoarsphenamine is administered by injection into a superficial vein, usually of the arm; the phial containing the selected dose should be sterilized by immersing it in alcohol, which also serves to detect leaks, and allowing it to dry. It is then broken and the contents poured at once into 5 or 10 c.c. of cool, sterile, distilled water in which they should dissolve rapidly. The solution must be injected *immediately* but slowly (during from 3 to 5 minutes) through a fine needle into the vein. Solutions should not be shaken and their temperature should not exceed 22° C. lest oxidation occur. The injections are best given when the stomach is empty, and the patient should be allowed to rest for some hours afterwards.

Modern Treatment of Syphilis.—The older methods of treating syphilis have been modified by Penicillin, which is a potent antisyphilitic and free from toxic effects. Penicillin injections abolish infectivity and cause the disappearance of spirochætes within 12 to 24 hours from primary chancres which heal in two weeks, and most secondary lesions heal in a few days, but even massive doses of Penicillin are not permanently curative. It is acknowledged that it is advisable to give, in addition to Penicillin treatment, courses of Neoarsphenamine and Bismuth, the latter, being slowly absorbed, maintains an antisyphilitic in the tissues during the intervals between the injections of the organic arsenicals which are excreted quickly. It is considered that Penicillin may have a synergistic or potentiating action on the effects of Arsenic and Bismuth and that a combination of the three drugs is the best treatment.

The routine for the treatment of primary and secondary syphilis by Penicillin, Neoarsphenamine or Oxophenarsine, and Bismuth varies in different clinics at present, but the system adopted will resemble the following schemes:

For **primary and secondary syphilis**, Penicillin is injected intramuscularly to a total dose of at least 4·5 mega-Units during the first eight days; this may be done, in hospital cases, by frequent intramuscular injections of aqueous Penicillin, or, in out-patients, by daily injections of 600,000 Units of Penicillin as the Oily Injection or as Procaine-Penicillin. On the third and seventh day of the first week, 0·3 G and 0·45 G respectively of Neoarsphenamine also are commonly given intravenously. Then, during the second to eighth week inclusive, the patient receives regular weekly doses of 0·6 G Neoarsphenamine, or 60 mg. of Oxophenarsine, intravenously, along with 0·2 G of Bismuth Oxychloride by intramuscular injection. At the end of the eighth week, a further week's dosage with Penicillin may be advised. For women, a maximal single dosage of 0·45 G of Neoarsphenamine or 40 mg. of Oxophenarsine is the usual.

Second courses are advisable after an interval of a month and all cases should be under serological observation for three years, the cerebro-spinal fluid being examined at least annually.

In many cases of early syphilis, Penicillin causes within 4 to 8 hours Jarisch-Herxheimer reactions of fever and exacerbation of the chancre or secondary skin rashes lasting for 48 hours, therefore some clinicians prefer to commence the treatment with Neoarsphenamine or Oxophenarsine during the first two weeks and give during the third week the daily course of Penicillin with the usual weekly dose of Neoarsphenamine or Oxophenarsine, but no Bismuth, and then resume the weekly Arsenical and Bismuth therapy from the fourth week onwards.

An intensive course, suitable for travelling members of the community, consists of 12 injections of 0·45 G of Neoarsphenamine, or 60 mg. (40 mg. for women) of Oxophenarsine intravenously with 0·12 G of Bismuth intramuscularly at intervals of

3 to 4 days, except during the third week of treatment when Penicillin daily in doses of 500,000 Units is given for six days as well as the bi-weekly dose of the Organic Arsenical, the Bismuth injections being omitted during this week. After such an intensive course, it is usual to withhold further treatment as long as the clinical and serological "follow-up" remains satisfactory.

In **maternal syphilis**, similar treatment with the three drugs has produced successful results in preventing infantile congenital syphilis, but to avoid strain on the maternal kidneys and the risk of arsenical encephalopathy to which pregnant women are more liable, the Arsenic and Bismuth injections are usually given consecutively and not simultaneously. Sometimes Penicillin alone is used with the object of protecting the fœtus, and, if toxic effects of Bismuth or Arsenic arise, Penicillin should be continued alone, further treatment of the mother being postponed till after delivery.

For **congenital syphilis** in a feeble infant, Penicillin is generally used first, but the initial doses must be cautiously increased to avoid Herxheimer intensifications. The *total* dosage spread over 12 to 14 days should be 80,000 Units per Kg. body weight (36,000 Units per lb. or 200,000 Units for a child of 5 lb. 10 ozs.); this may be given by repeated intramuscular injections, starting with 1,000 Units and slowly increasing, or more conveniently in infants under six months, by gradually increased oral administration (*see* p. 416).

Next a bi-weekly intramuscular course of Injectio Bismuthi, diluted with 9 parts of Injectio Dextrosi (i.e. 1 Mil = 20 mg. Bismuth) is given, starting with 1/3 Mil (6·6 mg. Bismuth) and increasing to 1/2 Mil; later 1 Mil is given once a week. This course may last a month or two.

If the child is improving, an Organic Arsenical in dilute solution is then given intramuscularly at weekly intervals commencing with very small doses (6·6 mg.) in the form of Sulpharsphenamine, or Acetylarsan (Diethylamine Acetarsol in 9·4 per cent. solution) and the doses slowly increased during six to eight weeks. The maximum dosage for infants of Sulpharsphenamine is 10 to 20 mg. per Kg. body weight (4·5 to 9 mg. per lb.). It may be desirable to repeat these courses and, in well-nourished infants, preliminary treatment with small doses of Bismuth or a diluted Arsenical may precede the Penicillin treatment.

In **tertiary syphilis** the objective is to prevent further spread of the disease and to resolve existing lesions without impairing the vital organs or the patient's health by producing severe reactions. As Penicillin is liable to provoke reactions, the preliminary treatment is with Potassium Iodide 2 G (30 gr.) daily and Bismuth Oxychloride 0·2 G by intramuscular injection each week for four weeks; this usually clears up gummatous nodules and ulcers. Penicillin in Oil or Procaine-Penicillin is then given daily for eight days in 500,000 Units dosage; and, thereafter, weekly injections of Neoarsphenamine starting with a dose of 0·3 G and increasing to 0·6 G are given for eight weeks, and sometimes followed by Bismuth injections for another four weeks.

Alternatively, 10 weekly injections of 0·12 G of Bismuth are given along with Potassium Iodide by mouth, then 10 weekly injections of Neoarsphenamine or Oxophenarsine, with an interpolated week of Penicillin injections of 500,000 Units daily.

Cases of **latent syphilis**, revealed by serological examination, should be started on Potassium Iodide orally and Bismuth injections weekly for a month, and then the routine course for early syphilis followed.

In **cardio-vascular syphilis**, arsenicals are not advisable and, even after preliminary treatment with Potassium Iodide and Bismuth, Penicillin should be started in small (30,000 Unit) doses daily and increased, if no untoward reactions follow, gradually to reach a total of 6 mega-Units.

Neurosyphilis responds very satisfactorily to Penicillin, which has now almost displaced Tryparsamide and malarial therapy, but it should be commenced in small doses, especially in meningovascular cases. Preliminary treatment with Iodides and Bismuth is essential if therapeutic shock is to be avoided.

Oxophenarsine Hydrochloride contains in its smaller dosage less Arsenic, is less toxic, and may be injected more rapidly than Neoarsphenamine, but it is equally effective and useful in the treatment of syphilis; it rarely causes more than mild reactions of gastro-intestinal type. The optimum *total* dosage of Oxophenarsine is 20 to 25 mg. per Kg. body weight, but, as this drug is quickly excreted, it is injected intravenously either daily in doses of 6 mg. for 20 days, or twice weekly in doses of 60 mg. for eight weeks in conjunction with Bismuth therapy. When given twice weekly it is usual to begin with 45 mg. for men and 30 mg. for women and to increase to 60 mg. and 40 mg. respectively; for children, 0·5 mg. per Kg. body weight is used.

It has been used also by intravenous drip of 0·24 G Oxophenarsine Hydrochloride in 2,000 Mils of 5 per cent. Dextrose at the rate of 3 Mils per minute; the treatment being repeated for five successive days.

Neo-halarsine is Oxophenarsine Tartrate. It is given intravenously in the average dosage of 90 mg. for men and 60 mg. for women in treating syphilis, either concurrently or alternating with Bismuth and in association with Penicillin. The powder or a 10 per cent. solution is applied locally for Vincent's infection.

Sulpharsphenamine is injected subcutaneously or intramuscularly, about 0·3 G being dissolved in 1 Mil of sterile distilled water. It is used in a similar routine and, although slower in action, is useful when the intravenous route cannot be utilized, and is particularly suitable for the treatment of infantile syphilis, the initial dosage being 0·005 to 0·01 G per Kg. body weight.

Actions of Organic Arsenicals in Syphilis.—After intravenous injection of Neoarsphenamine, the spirochætes disappear from the **primary lesions**, usually within a day, and are absent from the glands after about four days. The primary lesions often heal in a fortnight, although induration may persist longer; indurated chancres, owing to deficient blood supply, are more resistant.

In **secondary cases** with positive serum reaction, mucous lesions of the mouth and throat, as well as ulcers, heal within a few days and cutaneous rashes are cured.

Treatment is also very effective in **tertiary cases,** especially when combined with courses of Potassium Iodide; ulcers and lesions of the nasal septum improve quickly and the fœtor and ozæna disappear, while superficial nodules and gummata retrogress rapidly.

It must be emphasized that the treatment of syphilis should be commenced as soon as diagnosis is made and the patient impressed with the fact that the treatment must be pursued even though the lesions have healed; otherwise relapses will occur. Efficient early treatment with Penicillin, Arsenic and Bismuth will prevent late syphilis, but imperfect treatment may leave parasites latent in the tissues.

Organic Arsenicals in other Parasitic Diseases.—Injections of Neoarsphenamine are curative in frambœsia or yaws, relapsing fever, rat-bite fever, and bronchial spirochætosis; a single injection of 0·3 to 0·4 G often suffices to destroy the parasites but three at weekly intervals are usually given: if used early, injections are also curative in anthrax. Vincent's angina and tropical ulcer respond to local application of a 5–10 per cent. solution of Neoarsphenamine, but in severe cases an injection may be advisable.

Injections have also been found useful in cancrum oris, guinea-worm, and in malaria which is resistant to Quinine. Neoarsphenamine is less successful in trypanosomiasis than Tryparsamide.

Toxic Effects of Organic Arsenicals.—*Local Effects:* Accidental injection of Neoarsphenamine subcutaneously will cause severe inflammation and possibly necrosis; the part should be promptly aspirated and 10 c.c. of normal saline or a solution (0·6 per cent.) of Sodium Thiosulphate injected into the area (*see* p. 115).

General Effects: Slow intravenous injections rarely cause marked immediate actions; sometimes there is severe shoulder pain from endocardial irritation, and in the mouth a taste of garlic. Some toxic effects, not often alarming, are seen in from 5 to 10 per cent. of cases, but it is important to realize that most of these may be avoided by the use of reliable preparations, a rigid aseptic technique, and careful examination of cases before repeating dosage. The toxic effects may be arranged according to the time of their occurrence.

(1) *Vascular or Anaphylactoid Collapse* (*Nitritoid Crisis*).—This occurs during or soon after an injection; the face becomes flushed, the conjunctivæ reddened and œdematous, the pulse rapid and weak, the blood-pressure is lowered, and giddiness, nausea, vomiting, cyanosis, and a cold perspiration may follow; in severe cases, consciousness may even be lost. Recovery occurs in from quarter to half an hour and is hastened by a hypodermic injection of Adrenaline. Such collapse may also be averted by previous administration of Adrenaline, Ephedrine or Atropine. Vascular collapse is due to a physical reaction between the colloidal particles of the Arsphenamine and the blood or tissues, probably causing liberation of histamine; it is rare if the drug be injected slowly.

(2) *Febrile Reactions arising within one to four hours.*—These start with shivering and febrile response to 100° or 102° F., which is accompanied by headache, vomiting and diarrhœa, as well as aches or pains in the back and limbs. Occasionally itching and erythematous skin rashes occur and the urine may contain albumin and casts. These symptoms usually subside in 24 hours. They are sometimes the result of imperfectly distilled water, but may be due to the colloidal nature of the injection.

(3) *Delayed Febrile and Cutaneous Reactions.*—These develop after 24 hours and in many respects resemble the preceding symptoms; chancres, secondary and tertiary lesions may become

aggravated or "flare up" from liberation of spirochætal endotoxins (Jarisch-Herxheimer reactions).

(4) *Arsenical Poisoning.*—This may arise three days after the primary dose, but more commonly it occurs late in the course of treatment, owing to defective excretion of Arsenic. Erythematous eruptions are common, while desquamative or exfoliative dermatitis is also frequent. The development of **jaundice** indicates acute yellow atrophy or necrosis of the liver and is often followed by vomiting, hæmorrhagic enteritis and tubular nephritis: sometimes the hepatitis is of infective origin from an imperfectly sterilized syringe. The liver may be protected by ensuring adequate carbohydrate and protein reserves. Large doses, from injury to the cerebral vessels, may cause, particularly in young adults or pregnant women, hæmorrhagic encephalitis with symptoms of muscular twitching and convulsion of an epileptiform type, followed by coma and death. The toxic effects of Organic Arsenicals, especially the dermatitis, are effectively treated by Dimercaprol (*see* p. 383).

Excretion of Organic Arsenicals.—When injected intravenously, the bulk of the Neoarsphenamine disappears from the blood in three or four hours; it is adsorbed by the reticulo-endothelial tissues and hence we find it stored in the spleen, liver, lungs and kidneys. Excretion starts in the urine within a few minutes, reaches a maximum in the first or second day and is small after the fourth day. Smaller amounts, excreted by the bile, are found in the fæces after the third day. The excretion of the pentavalent compounds is much more rapid than that of the trivalent arsphenamines.

Tryparsamidum.—Tryparsamide. Sodium N-phenylglycinamide-*p*-arsonate.

CHARACTERS.—A colourless, crystalline powder. *Solubility.*—Freely in water. Contains 25% of Arsenic.

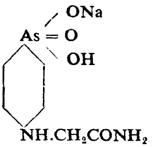
Dose.—*By subcutaneous, intramuscular or intravenous injection.*
Metric, 1 to 2 G; Imperial, 15 to 30 gr.

Preparation

Injectio Tryparsamidi.—A sterile solution in Water for Injection, prepared from the contents of a glass phial immediately before use.

ACTIONS AND USES

Tryparsamide is valuable in the treatment of African **sleeping sickness.** The dose is given in 10 Mils of sterile distilled water by intravenous injection once a week and treatment rapidly clears the blood of trypanosomes (T. gambiense) and is curative in early infections, but does not eradicate T. rhodesiense. Since it penetrates even nervous tissue better than other Arsenical compounds, it is also successful in curing a number, of cases where the nervous system is involved, whilst some advanced cerebro-spinal cases show definite improvements.



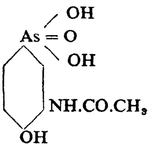
Tryparsamide is not of value in primary or secondary syphilis, but in **neurosyphilis** it produces more rapid improvement and benefit than Neoarsphenamine although it is much less toxic to the treponema. It is of most value in early paretic cases, but its use is rapidly being displaced by Penicillin (*see* p. 412). In dementia paralytica, a long series of injections was necessary and its effects were enhanced when used after pyrexial therapy by malarial inoculation but, owing to Penicillin therapy, these means are now less commonly used.

Toxicity of Tryparsamide.—Its general toxicity is low but, like Atoxyl, it may produce visual impairment which is commonly temporary but may be permanent; perimeter charts should be made regularly during treatment.

Acetarsol.—Acetarsol. "Stovarsol." 3-acetylamino-4-hydroxyphenylarsonic acid.

CHARACTERS.—A white crystalline powder; almost insoluble in cold water; soluble in dilute alkalis. Contains 27% of Arsenic.
Dose.—Metric, 60 to 250 mg.; Imperial, 1 to 4 gr.

Acetarsol is of value when given as tablets by mouth thrice daily in chronic amœbic dysentery which resists Emetine, or may be ordered in the weekly intervals between courses of Emetine. For giardiasis (lambliasis) a week's treatment may suffice. It has also been recommended for resistant cases of tertian malaria, Vincent's angina and frambœsia. As a prophylactic after syphilitic risk, it is unreliable and may postpone the primary lesion. It may be used to treat congenital syphilis. As a pessary, or insufflated as a dusting powder (10 per cent. with Kaolin), it is useful in vaginal infection with Trichomonas vaginalis.



Toxic Symptoms are headache, vomiting, diarrhœa, erythema, and exfoliative dermatitis.

Carbarsonum.—Carbarsone. *p*-Carbaminophenylarsonic acid $C_6H_4As{:}O{:}(OH)_2.NH_2CONH$.

CHARACTERS.—White crystals, insoluble in water, soluble in alkaline water.
Dose.—Metric, 0·12 to 0·2 G; Imperial, 2 to 3 gr.

Carbarsone is less toxic to the host and more toxic to the dysenteric amœbæ than Acetarsol. It is given orally twice daily for 10 days and the course may be repeated after 10 days' interval; or, if this fails, enemas (200 Mils) of 1 per cent. Carbarsone in 2 per cent. Sodium Bicarbonate are given in the evenings, along with a hypnotic, until five have been retained by the bowel. Carbarsone is safe in clinically useful doses.

Stabilarsan.—(*Not official*) Arsphenamine diglucoside.
CHARACTERS.—A light-yellow powder, stable in air; supplied in ampoules containing a 10% solution in 50% glucose.
Dose.—*Intravenously*: **0·45 to 0·6 G (6½ to 10 gr.)**

USES

Stabilarsan has a low toxicity and is suitable for syphilitic treatment and for intramuscular administration in congenital syphilis in dose of 0·035 G per lb. body-weight.

Biological Tests for Arsphenamines.—(a) *For absence of undue toxicity:* By the intravenous injection with a 2% solution in distilled water of 10 mice with a dose *x* of the Neoarsphenamine under test, and of 10 mice with a dose 1·20 *x* of the Standard Preparation kept in the National Institute for Medical Research, the latter dose being that which will be lethal to about 50% of the mice; the mice are observed for three days. If the number killed by the sample under test is not greater than that killed by the Standard Preparation, the sample is satisfactory. For Sulpharsphenamine, the method is the same but the injections are made subcutaneously.

(b) *For therapeutic efficacy:* The Neoarsphenamine under test must in a dose *x* possess a curative action not less than a dose 0·8 *x* of the Standard Preparation when both are injected intravenously as 0·1% solutions into mice infected with Trypanosoma equiperdum. The blood of of the mice is examined on the first and third days to ascertain if it is cleared of trypanosomes. For Sulpharsphenamine, the method is the same but a 0·2% solution is injected subcutaneously and the blood examined on the third and fourth days.

It must also cause no œdema or necrosis when injected subcutaneously into rats.

ANTIMONIUM. ANTIMONY. Sb. 121·76

The Antimony ion is toxic to certain protozoa; the soluble double salts are gastric irritants and, therefore, reflex expectorants and emetics.

1. Antimonii et Potassii Tartras.—Potassium Antimonyl Tartrate. Tartar Emetic. $[K(SbO)C_4H_4O_6]_2H_2O$.

CHARACTERS.—Colourless, transparent crystals or powder; taste, sweet, metallic. *Solubility.*—1 in 17 of water.

Dose.—*Expectorant:* **Metric, 2 to 8 mg.; Imperial, 1/32 to 1/8 gr.**
Emetic: **Metric, 30 to 60 mg.; Imperial, 1/2 to 1 gr.**
Intravenously: **Metric, 30 to 120 mg.; Imperial, 1/2 to 2 gr.**

Preparation

Injectio Antimonii et Potassii Tartratis.—A sterile solution in Water for Injection; contains 20 mg. (1/3 gr.) in 1 Mil (15 min.).

2. **Antimonii et Sodii Tartras.**—Sodium Antimonyl Tartrate. $Na(SbO)C_4H_4O_6$.

CHARACTERS.—Colourless hygroscopic scales or powder; taste sweetish. *Solubility.*—1 in 1·5 of water.

Dose.—*Expectorant:* **Metric, 2 to 8 mg.; Imperial, 1/32 to 1/8 gr.**
Emetic: **Metric, 30 to 60 mg.; Imperial, 1/2 to 1 gr.**
Intravenously: **Metric, 30 to 120 mg.; Imperial, 1/2 to 2 gr.**

Preparation

Injectio Antimonii et Sodii Tartratis.—A sterile solution in Water for Injection; contains 60 mg. (1 gr.) in 1 Mil (15 min.).

ACTIONS AND USES

Externally.—Tartar Emetic, applied to the skin in solution or as an ointment, is an irritant, producing first an erythema and, later, around the sweat and sebaceous glands, a crop of pustules which coalesce to form abscesses. As a counter-irritant it is obsolete.

Internally.—In the stomach, small doses of Antimony salts are irritant to the mucous membrane; this irritation is conveyed by the sensory fibres of the vagus to the medullary centres, and there is produced reflexly increased salivary and bronchial secretion, perspiration and feeling of nausea. Because they increase and liquefy the secretion of bronchial mucus, small doses of Antimony salts are used as **expectorants,** particularly in acute bronchitis with tenacious sputum. Similar doses by increasing perspiration act as **antipyretics** but they are unreliable and depressing.

In larger doses the more powerful irritation in the stomach produces reflexly severe nausea, a feeling of coldness with profuse perspiration, an increased rapidity but weakening of both pulse and respiration, a fall in blood-pressure and, finally, repeated emesis. As **reflex emetics** Antimony salts are slow as well as uncertain in action and cause also nervous prostration from prolonged nauseation; therefore they are not suitable for removing poisons.

In the intestine Antimony preparations continue to be irritant and, if large doses are not vomited, they will produce enteritis, pain and diarrhœa by an action resembling that of Arsenic.

Actions and Absorption.—Antimony is absorbed from the small intestine and, like Arsenic, influences metabolism, which is increased, in association with defective oxidation, by large and continued dosage; ultimately fatty degeneration of the liver and other tissues occurs. These effects are of no therapeutic importance. Antimony is excreted more rapidly than Arsenic and chiefly through the large intestine, by the bile, the kidneys and skin.

Antimony Salts in Protozoal Diseases.—Both trivalent and pentavalent antimonial preparations are valuable in protozoal diseases. Either Sodium or Potassium Antimonyl Tartrate in doses of 0·03 G (1/2 gr.) increasing to 0·12 (2 gr.) is injected intravenously in 1 or 2 per cent. solution twice weekly until 2 or 3 G have been given. Such injections are curative in kala-azar and other leishmania infections, such as oriental sore and espundia. Very successful results have also been obtained by giving injections on alternate days in bilharziasis (schistosomiasis) and in filariasis, where the Antimony salt is quickly effective in killing the ova and larvæ respectively, but relapses will occur unless treatment is continued until the parent worm (Bilharzia or Filaria) succumbs. Antimony is specific also for granuloma inguinale. Injections of Antimony were found of value only in early cases of trypanosomiasis, before the nervous system was involved; hence Tryparsamide is now preferred; in relapsing fever and yaws, Arsenical preparations are better.

Toxic Effects.—Overdosage with Antimony salts intravenously may cause nausea, an irritable cough, salivation with metallic taste, and abdominal pains with diarrhœa.

Stibophenum.—Stibophen. Fouadin. Sodium Antimony-bispyrocatechol-sodium Disulphonate. $C_6H_2(NaSO_3)_2O_2 : Sb.O(NaSO_3)_2NaO.C_6H_2, 7H_2O$.

CHARACTERS.—Colourless, fine crystals; easily soluble in water, turning yellowish if neutral.

Dose.—*By intravenous injection:*

Metric, 0·1 to 0·3 G; Imperial, 1½ to 5 gr.

Preparation

Injectio Stibopheni.—Stibophen 6·4% with Sodium Metabisulphite in Water for Injection; 5 Mils (75 min.) contain 0·3 G (5 gr.).

Dose.—*By intravenous injection:*

Metric, 1·5 to 5 Mils; Imperial, 25 to 75 min.

ACTIONS AND USES

Stibophen is given intravenously in doses of 1·5 Mils increasing to 5 Mils on alternate days for a course of ten injections in all types of schistosomiasis (bilharziasis) and for leishmaniasis (kala-azar and oriental sore). Stibophen may cause nausea, vomiting, abdominal pain, muscle cramps, and liver necrosis (yellow atrophy).

Sodium Stibogluconate (B.P.C.).—*Dose.*—Intramuscularly or intravenously 0·6 to 2 G (10 to 30 gr.) in a 30% solution in Water for Injection. This is used to treat leishmaniasis (kala-azar) by daily injections of 6 Mils of the solution. It is less toxic and irritant than the Antimonyl Tartrates and is rapidly excreted. It can be used intramuscularly for children, and in small amounts the solution is injected locally around oriental sore.

Urea Stibamide (B.P.C.).—*Dose.*—By intravenous injection: 0·06 to 0·2 G (1 to 3 gr.) in 5% solution in Water for Injection daily or on alternate days for a course of twelve injections. It is not given intramuscularly as it causes pain and necrosis. It is used for leishmania infections and seldom causes severe reactions although a fall in blood-pressure may occur.

Lithium Antimony Thiomalate.—Anthiomaline. This is given in 6% solution intramuscularly every second day in dose of 1 Mil increasing to 4 Mils, and then twice or thrice weekly for schistosomiasis and granuloma inguinale; half doses are suitable for children.

OTHER DRUGS USED IN TRYPANOSOMIASIS

Suraminum.—Suramin. Bayer 205. Germanin. The symmetrical urea of the sodium salt of Benzoyl-amino-methylbenzoyl-aminonaphthalene-trisulphonic acid.

CHARACTERS.—A white, or creamy, hygroscopic powder; easily soluble in water; taste bitter. Must be tested for undue toxicity and therapeutic (trypanocidal) potency.

Dose.—*By intravenous injection:*

Metric, 1 to 2 G; Imperial, 15 to 30 gr.

Preparation

Injectio Suramini.—A sterile solution in Water for Injection prepared from the contents of a glass phial *immediately* before injection.

ACTIONS AND USES

Suramin is given in trypanosomiasis by intravenous injection in 10 per cent. solution, commencing with a dose of 0·5 G in order to test the patient's tolerance; then doses of 1 G are given on two or three consecutive days, and two more at intervals of a week. After this course, six to eight weekly injections of Tryparsamide are commonly given. One intravenous dose of 2 G (30 gr.) acts as a prophylactic for three months against trypanosomiasis, but may keep an infection latent. Suramin clears the peripheral blood of trypanosomes in twenty-four hours and is valuable in early cases, but it does not penetrate the cerebro-spinal fluid, therefore cases in which the nervous system is involved are not improved. Suramin is more effective against T. rhodesiense than against T. gambiense.

Suramin may readily cause albuminuria, necessitating reduction of the dose to avoid renal damage; nausea, vomiting and skin rashes occur, while amblyopia and peripheral neuritis are further toxic effects.

Pentamidine Isethionate (B.P.C.)

Dose.—*Intramuscularly or intravenously*: 0·15 to 0·3 G (2½ to 5 gr.) or 3 to 4 mg. per Kg. body weight in 10% solution daily or on alternate days.

ACTIONS AND USES

Pentamidine is a trypanocide, but does not enter the cerebrospinal fluid; it is, therefore, useful only in early cases. Intramuscular injections are painful and may cause local necrosis; intravenous injections cause a severe fall in blood-pressure, hence the patient should be in bed. Single injections at six-monthly intervals are used as prophylactics against trypanosomiasis. For early cases, usually 10 injections are given as a course on successive or alternate days; it is also useful for leishmaniasis (kala-azar), if Antimony treatment fails.

Stilbamidine Isethionate by intravenous injection of 3 to 4 mg. per Kg. body weight is used in myelomatosis, but also causes a rapid drop in blood-pressure.

SULPHUR. SULPHUR. S. 32·06

Sulphur is inert; it acts after conversion into sulphides which are parasiticides and irritants.

1. **Sulphur Sublimatum.**—Sublimed Sulphur. Flowers of Sulphur.

CHARACTERS.—A fine, yellow, gritty powder; insoluble in water.
Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparations

1. **Unguentum Sulphuris.**—Sublimed Sulphur 10% in Simple Ointment.
2. **Pulvis Glycyrrhizæ Compositus.**—Contains 8% (*see* p. 143).

2. **Sulphur Præcipitatum.**—Precipitated Sulphur. Milk of Sulphur.

CHARACTERS.—A greyish-yellow, soft, amorphous powder; tasteless; insoluble in water.

Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

ACTIONS AND USES

Externally.—Sulphur, when burned, evolves sulphur dioxide gas which, by acting as a reducing agent, is an active **disinfectant.** For the disinfection of rooms and bedclothes, 3 lb. of Sulphur are necessary for each 1,000 cubic feet of space, the room being kept closed for some hours. Sulphur dioxide is also effective for destroying vermin, but has the disadvantage of being a bleaching agent.

When Sulphur Ointment is rubbed into the skin the Sulphur is partially converted by the cutaneous secretion into sulphides and sulphuretted hydrogen, which are **antiseptics, parasiticides and mild irritants.** Sulphur Ointment was very commonly used in the treatment of itch or **scabies** because it kills the Acarus (Sarcoptes) scabiei; the affected parts must first be scrubbed well with soft soap and hot water to open up the burrows, and then the ointment should be thoroughly massaged into them. Sulphur Ointment is also employed in the treatment of acne, eczema, seborrhœa, ringworm of the scalp and other **skin diseases**, but it may easily irritate delicate skins. Barium Sulphide, diluted with 2 or 3 parts of starch and made into a paste, renders hair gelatinous and is a depilatory, but it irritates and must be washed off in five minutes.

Internally.—Sulphur passes through the stomach unaltered and produces no effects there. In the intestine it is partly converted into alkaline sulphides and sulphuretted hydrogen which exert a mild irritant action on the mucous membrane: the irritation excites a moderate increase in peristalsis, chiefly in the colon, and Sulphur therefore acts as a **laxative.** It causes, after about 10 to 12 hours and without griping or colic, the evacuation of a soft, formed stool, which smells of sulphides. As a laxative, Compound Liquorice Powder is readily taken by children and is often employed in their slight forms of constipation.

Actions after Absorption.—When Sulphur is taken internally, small amounts of sulphides are absorbed but have no important effects; they are excreted mainly in the urine as sulphates, but traces, as sulphides, are excreted by the bronchial and sweat glands, giving to the breath and perspiration the odour of sulphuretted hydrogen.

Sulphides in the form of Natural Sulphur Waters are often advised internally, and as baths externally, for the treatment of chronic muscular and articular rheumatism, uric acid diathesis, and gout, and of various skin diseases such as acne, psoriasis, and chronic eczema. There is no evidence of specific effect but the hygienic treatment improves some cases. The important sulphur spas are Harrogate, Strathpeffer, Llandrindod, and Llanwrtyd in Great Britain, and Aix-les-Bains, Aachen, Challes, and Bagnères-de-Luchon on the Continent.

Mesulphenum (B.P.C.).—Mitigal.—Dimethyl-diphenyl-disulphide, a yellow oil applied, after scrubbing the affected area, for three successive evenings, is valuable for scabies, pediculosis and acne.

Sodii Thiosulphas (B.P.C.).—Sodium Hyposulphite. $Na_2S_2O_3,5H_2O$. Colourless, efflorescent crystals, taste saline. *Solubility*.—2 in 1 of water. *Dose*.—By subcutaneous, intramuscular or intravenous injection, Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

Sodium Thiosulphate is used externally as an antiseptic lotion, 10%, for parasitic skin diseases.

Intravenously injected, 0·5 G in 5 or 10 Mils of sterile water, it was formerly used as an **antidote** for poisoning from Neoarsphenamine, Mercury or Bismuth arising during syphilitic treatment and from Gold compounds, but Dimercaprol (*see* p. 383) is much more effective. If an Arsphenamine injection escapes into the perivenal tissues, aspiration, followed by the injection of 0·5 G Thiosulphate in 10% solution will alleviate painful reactions. It is injected intravenously (10 to 50 Mils of 20% solution) to form Sulphocyanides in cyanide poisoning. Tablets, 15 mg. (1/4 gr.) tinted blue, are used to annul the taste of chlorine when this is used to sterilize water for drinking.

Sodii Metabisulphis.—Sodium Metabisulphite. $Na_2S_2O_5$.

CHARACTERS.—Colourless crystals or white powder; odour sulphurous, taste acid and saline; slowly oxidizes in air to sulphate.

ACTIONS AND USES

Sodium Metabisulphite is used as an antioxidant in the Injections of Adrenaline, Apomorphine Hydrochloride, Physostigmine Salicylate, Strong Procaine and Adrenaline, and Stibophen, and in Liquor Adrenalini Hydrochloridi.

CHLORUM. CHLORINE. Cl. 35·46

Free Chlorine is an antiseptic.

Calx Chlorinata.—Chlorinated Lime. $CaCl_2O_2,CaCl_2$ or $CaOCl_2$. A compound of Calcium Hypochlorite and Calcium Chloride.

CHARACTERS.—A dull-white powder; odour chlorinous; becomes moist and decomposes on exposure; partially soluble in water. Contains 30% available Chlorine.

Preparation

Liquor Sodæ Chlorinatæ Chirurgicalis.—Surgical Solution of Chlorinated Soda. Dakin's Solution.

SOURCE.—Made by dissolving 3·76 Sodium Carbonate in 100 Distilled Water and adding this solution to 1·88 of Chlorinated Lime (30% Cl); decant after standing and add 0·4 Boric Acid. These percentages are varied with the amount of Cl available in the Chlorinated Lime.

CHARACTERS.—A yellowish fluid, smelling of Chlorine. It loses strength in light, warmth and air. It should be recently prepared.

Chloramina.—Chloramine. Chloramine-T. Sodium *p*-toluene-sulphonchloroamide. $CH_3.C_6H_4.SO_2Na:NCl.3H_2O$.

SOURCE.—By the action of Sodium Hypochlorite solution on *p*-toluenesulphonamide.

CHARACTERS.—White, crystalline powder; odour and taste chlorinous; loses Chlorine and becomes yellow on exposure. *Solubility.*—1 in 7 of water.

ACTIONS AND USES

Externally.—**Hypochlorites as Disinfectants.** Solutions of Hypochlorites or Hypochlorous Acid are valuable disinfectants and **antiseptics** because: (1) their available Chlorine readily unites with the amine groups of proteins, e.g. in bacteria, to form Chloramines; this reaction is bactericidal; (2) these Chloramines are soluble, and therefore Hypochlorites **dissolve organic matter,** necrosed tissues and bacteria—except the tubercle bacillus, which is protected by its fatty envelope; (3) they are powerful **deodorants** and also **bleaching agents.**

Calx Chlorinata and solutions of Sodium Hypochlorite (2·5 to 10 per cent. available Chlorine) are employed as disinfectants for the stools of typhoid, cholera, etc., prior to their disposal. Hypochlorites, having from 1 to 5 per cent. available Chlorine, are largely used as disinfectants, deodorants and solvents for bacteria and organic matter in sanitary utensils, drains, etc., and still weaker strengths (0·1 per cent. Cl) for swabbing floors and for laundry services. Chloramine is a prophylactic and antidote to the effects of "Mustard Gas," Lewisite and Diethylchlorarsine on the skin.

Hypochlorites are valuable means of disinfecting swimming-baths and polluted waters. The amounts required vary with the amount of organic matter polluting the water but a surplus of 0·25–1 part of free Chlorine per million of water should be allowed for safety. **Chlorination** is particularly effective in destroying coliform bacilli and other intestinal organisms, e.g. typhoid.

Halazone, *p*-sulphondichloroamido-benzoic acid, is used to sterilize water for drinking. A tablet of 15 mg. (1/4 gr.), added to two pints of water sterilizes it in 30 minutes. A crystal or tablet (15 mg.) of Sodium Thiosulphate removes any remaining taste of Chlorine.

Hypochlorites as Wound Antiseptics.—When applied to wounds Hypochlorite solutions readily liberate their available Chlorine, and this rapidly unites with the amine groups of proteins to form Chloramines which, being also unstable, continue slowly to liberate free Chlorine. The union of the Chlorine with the amine groups of bacterial proteins causes the death and solution of most bacteria within the first few minutes but, as the Chlorine also unites with and dissolves the proteins of necrosed tissue, pus cells and serum exudates, its bactericidal power is speedily exhausted; the small amounts of Chloramine formed have only a slight antiseptic action, so that when the primary bactericidal action ceases, growth of uninjured bacteria in the wound is unchecked. Obviously, therefore, the best way of effecting sterilization of an infected wound with Hypochlorite solutions is by frequent saturation of the wound with fresh Hypochlorite solution, which can be conveyed into the pockets of the wound by tubes passing through the dressings so as to avoid frequent disturbances of the bandages (**Carrel-Dakin Irrigation**).

The Liquor Sodæ Chlorinatæ Chirurgicalis or Dakin's Solution, which contains about 0·5 per cent. available Chlorine, is a satisfactory wound antiseptic. It has a speedy, if evanescent, toxic action on the bacteria and rapidly cleans an infected wound from necrotic tissue; further, being isotonic, it is neither irritant nor toxic to the tissue cells. It stimulates the formation of healthy granulations, and the Boric Acid in it has a slight bacteriostatic action. Dakin's Solution is an excellent general antiseptic for casualty cases and burns, for syringing of abscesses and fistulas and for douching the vagina. It may be diluted to half-strength or less when employed by irrigation as an antiseptic and cleansing agent for burns enclosed in the Bunyan-Stannard envelope. It is also useful as a mouth-wash and gargle in stomatitis and infections of the fauces.

Eusol, made by macerating Calx Chlorinata 1·25, and Boric Acid 1·25, in water to 100 and decanting, has similar uses but it is somewhat irritant to epithelial tissues.

Chloramine-T.—When Chloramine-T solutions come into contact with organic matter, they slowly give up Chlorine. The antiseptic action is therefore less rapid than that of Dakin's

Solution but is more prolonged. As a general surgical antiseptic, solutions of 2 to 4 per cent. are employed for infected wounds, while for mouth-washes and urethral or vaginal irrigations, strengths of 0·25 to 1 per cent. are suitable. Clinically it has the advantage of being neither toxic nor irritating and solutions keep better. Chlorinated Cresols are also used (*see* p. 425).

IODUM. IODINE. I. 126·92

The Iodine ion is a halogen antiseptic, but Iodides have specific effects on various tissues.

1. **Iodum.**—Iodine. A solid, non-metallic element.

CHARACTERS.—Rhombic prisms or plates of bluish-black colour with metallic lustre and a peculiar odour. *Solubility.*—1 in 5,000 of water; freely in alcohol, chloroform, ether, carbon disulphide, or watery solutions of iodides.

Preparations

1. **Liquor Iodi Aquosus.**—Aqueous Solution of Iodine. Lugol's Solution. Iodine 5% with Potassium Iodide 10% in Water.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min. (diluted).
2. **Liquor Iodi Fortis.**—Strong solution of Iodine. "Tinctura Iodi Fortis." Iodine 10%, with Potassium Iodide 6% and Water 10% in 90% Alcohol.
3. **Liquor Iodi Mitis.**—Weak solution of Iodine. "Tinctura Iodi Mitis." Tincture of Iodine. Iodine 2·5%, with Potassium Iodide 1·5% and Water 2·5% in 90% Alcohol (contains 85% Alcohol).
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min. (diluted).

2. **Potassii Iodidum.**—Potassium Iodide. KI.

CHARACTERS.—White, cubical crystals or powder; taste saline. *Solubility.*—1 in 0·7 of water; 1 in 12 of alcohol 90%. *Incompatibles.*—Spiritus Ætheris Nitrosi, Potassium Chlorate and Liquor Strychninæ Hydrochloridi.
Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

3. **Sodii Iodidum.**—Sodium Iodide. NaI.

CHARACTERS.—A white, crystalline, deliquescent powder; taste saline. *Solubility.*—1 in 0·5 of water.
Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

ACTIONS AND USES

(1) **Iodine.** *Externally.*—Solutions containing free Iodine act like Chlorine by uniting with the amine groups of proteins, but the Iodamines are insoluble. These preparations are therefore active **disinfectants** and **antiseptics** but their bactericidal action is much reduced by proteins and is slower although more lasting

than that of Chlorine. As a disinfectant for the skin prior to injections or operations, Liquor Iodi Mitis is satisfactory; its rapidity of action is due, however, mainly to the alcohol. It is also used as an emergency application to small wounds but is painful; it is employed to disinfect catgut. Liquor Iodi Mitis is commonly applied as a paint in treating ringworm. Solutions of Iodine produce on the skin brown stains which may be removed by solutions of Ammonia or Sodium Hyposulphite.

Free Iodine in solutions of Potassium Iodide, when left in contact with the skin, is partly absorbed and irritates sensory nerve endings, causing tingling and a sense of heat in the part followed by reflex dilatation of superficial vessels—a **rubefacient action.** Too frequent applications may cause blistering. For this moderate but continued stimulant action on the skin either the Strong or Weak Liquor is used as a counter-irritant for chilblains, rheumatic neuritis and for subacute and chronic inflammations of joints, periostitis, lymphadenitis, etc. The Iodine absorbed locally exerts also a **resolvent action** on superficial cellular infiltrations and chronically inflamed tissues. Colourless or stainless preparations of Iodine are compounds of the element and do not have the actions of free Iodine.

Internally.—Liquor Iodi Mitis is painted on the gums as an antiseptic prior to injections; it is also useful for localized gingivitis, and is an efficient counter-irritant to the gums in dental periostitis. It is employed diluted (one part in 50 to 100 of water) as a mouth wash or gargle for stomatitis and tonsillitis. Sprays containing 1 per cent. of Iodine in Liquid Paraffin are of value in purulent nasal catarrh, and solutions of Iodine (0·5 per cent.) in alcohol are used as "dry" inhalations from masks for bronchial infections.

In the stomach small doses of Liquor Iodi Mitis cause mild irritation of the gastric walls, increase their vascularity and stimulate appetite; they are given diluted with water and sometimes serve to check recurrent vomiting. Large doses provoke pain, vomiting and, later, diarrhœa. In the stomach and bowel, free Iodine is converted into Iodides or protein compounds.

(2) **Iodides of Potassium and Sodium.** *Internally.*—Iodides, unless given in dilute solutions, may by salt action cause nausea and reflex vomiting. Being soluble and readily diffusible, they are absorbed quickly from the small intestine and penetrate freely all tissues of the body.

When given to susceptible persons in small doses or to normal individuals in large doses, they cause poisonous symptoms (iodism) which explain some of their therapeutic uses.

The **symptoms of iodism** are an objectionable metallic taste in the mouth, nasal congestion with a profuse watery secretion from the nasal mucosa; redness of the conjunctiva and lachrymation; pain over the frontal sinuses; swelling and redness of the gums, palate and fauces, accompanied by profuse salivation, a coated or raw tongue and aching in the temporo-maxillary joints; there is further a sense of heat and rawness in the trachea and chest, accompanied by cough and expectoration of a thin frothy mucus. Iodides also commonly cause **skin rashes** due to traces being excreted by the skin; the eruptions are of an erythematous, acneiform or papular character but may develop into vesicles and pustules or even ulcers; more rarely types resembling pemphigus or purpura are seen.

Iodides also increase the formation of thyroxine and this explains the occurrence of rapid pulse, palpitation, nervous symptoms and loss of weight during their use.

The "catarrhal" symptoms are due to a local stimulation of the glands in mucous membranes by the Iodides during their excretion; the suggestion that Iodides are decomposed with the liberation of free Iodine by means of the carbon dioxide in the tissues is untenable.

These symptoms explain only some of the valuable therapeutic effects of Iodides now to be discussed.

(1) **Expectorant Action.**—As, during excretion, they directly increase and liquefy the secretions of the bronchial glands, Iodides are valuable expectorants in bronchial catarrhs when secretion is tenacious or the mucous membrane dry or inflamed. Small doses are effective and may be combined with Ammonium Bicarbonate. Iodides act probably in the same way to give relief in spasmodic asthma.

(2) **Thyroid Diseases.**—Small doses of Iodides, which may be mixed with table salt (0·01 per cent.) or given at intervals, are employed in the prevention and treatment of simple goitre with remarkable benefit. Doses of 2 gr. daily suffice to increase thyroxine secretion and to reduce the hyperplasia of the gland, but the effects must be carefully watched because excessive dosage may readily cause symptoms of hyperthyroidism, namely loss of weight, rapid pulse and nervousness. Cases of simple goitre which do not respond to Iodides often improve on small doses of Iodine with Iodides in the form of the Liquor Iodi Aquosus. If this fails

to cause improvement, it suggests that the glandular cells are diseased, when administration of Thyroid is indicated.

Liquor Iodi Aquosus (Lugol's Solution), in doses between 10 and 20 min. taken in milk daily, diminishes the symptoms of nervousness, tremor, rapid pulse, and proptosis in thyrotoxicosis, and lowers the basal metabolic rate so that the weight increases; the maximal effect is reached within fourteen days. In hyperthyroidism this treatment may effect a symptomatic cure, and it is advisable for ten days before and some weeks after thyroidectomy. Small doses of Iodides will produce similar effects. Histologically the gland alters from a hyperplastic to a colloid state, decreases in vascularity, becomes firmer and less prominent (*see* Thiouracil, p. 203).

(3) **High Blood-pressure.**—Iodides are of distinct benefit in some cases of high blood-pressure as well as in arterio-sclerosis and in aneurysm. The explanation is obscure; it is not due to diminished viscosity of the blood or to vascular dilatation but, as atheromatous changes are frequently associated with myxœdema, the Iodides may counteract these by promoting an efficient secretion of thyroxine.

(4) **Tertiary Syphilis.**—Iodides are not toxic to the Treponema pallidum. They have, however, a value in primary and secondary syphilis to aid the resolution of indurated areas, and are invaluable in tertiary syphilis to promote the absorption of gummata. This absorptive effect may depend on the facts that Iodides lower the antitryptic power of serum, and that the Iodides convert unsaturated lipoids, which are antitryptic, into saturated forms which do not resist enzyme autolysis; thus the Iodides, which diffuse readily into pathological tissues, may promote their absorption both by increasing the autolytic power of serum and also by lowering the resistance of the tissues to enzyme action. Such an action may also permit more efficient access of more active antisyphilitics—Penicillin, Organic Arsenicals or Bismuth—to the spirochætes in indurated areas. Tertiary syphilitic lesions, such as nodes and other superficial enlargements, gummata of the brain and viscera, syphilitic disease of bones and joints and tertiary ulcers, as well as certain tertiary skin diseases, undergo rapid improvement, and even cure, from treatment with Iodides by mouth, especially when they are associated with injections of spirochæticides like the Organic Arsenicals, Penicillin, or Bismuth. They are often given before and between courses of Arsenic in the treatment of syphilis.

Iodides are also of service in cardio-vascular syphilis and in syphilitic headache and neuralgia, but they are of less value in neurosyphilis.

(5) In **chronic rheumatism**, gout, fibrositis and gonorrhœal arthritis, a course of Iodides often produces marked benefit. The action is probably again a resolvent one upon chronically inflamed tissues.

(6) Large doses of Iodides (60 to 120 gr.) daily are of great value in the treatment of **actinomycosis**, sporotrichosis and blastomycosis. Coccidoidal granuloma is also improved.

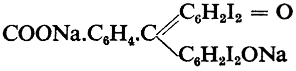
(7) Iodides are useful to mobilize and increase the excretion of Lead and Mercury in chronic poisoning by these metals, but their use may arouse symptoms because their efficacy depends on the solvent action of Iodides upon Albuminates of Lead and Mercury.

Excretion of Iodides.—Iodides being rapidly absorbed and diffusible, their excretion commences in from ten to twenty minutes, reaches a maximum in about four hours, but declines slowly. After a single dose (1 G) by mouth, 80 per cent. is excreted within 24 hours and the remainder within 48 hours (renal efficiency test). The main excretion occurs through the kidneys; smaller amounts of Iodides are excreted in the saliva, nasal and bronchial secretions, by the bowel and liver, and even by the milk and skin.

IODINE COMPOUNDS IN RADIOGRAPHY

Iodophthaleinum.—Iodophthalein. Disodium salt of Tetraiodo-phenolphthalein.

CHARACTERS.—A blue, crystalline powder; odourless; taste, saline, astringent. *Solubility.*—1 in 7 of water.



$$COONa.C_6H_4.C\begin{cases} C_6H_2I_2 = O \\ C_6H_2I_2ONa \end{cases}$$

Dose.—Metric, 40 to 60 mg. per Kg. body weight up to 5 G.
Imperial, 1/3 to 1/2 gr. per pound body weight up to 75 gr.
Intravenously (not official):
Metric, up to 3 G; Imperial, up to 45 gr.

ACTIONS AND USES

Iodophthalein is absorbed from the small intestine and is excreted into the bile. In the gall bladder, absorption of water from the bile leads to concentration of the dye, which **renders the gall bladder opaque to the passage of X-rays**. In practice, a purgative, usually Castor Oil, is given to promote emptying of the gall bladder; then at intervals during a light, fat-free meal on the following day, the Iodophthalein is given up to the suitable dose as a powder or in gelatin capsules. The radiograms exhibit the highest opacity about 15 hours afterwards.

Intravenous administration may be employed where oral dosage is impracticable; the dose of 3 G for patients weighing about 60 Kg (140 lb.) is dissolved in from 25 to 40 Mils of water and given in the morning as two slowly administered injections separated by half an hour. The intravenous route affords better shadows, but unpleasant reactions are not uncommon and care must be taken that the solution does not escape from the vein, as it is very irritant. Radiograms are taken at the 5th, 8th and 24th hours after.

Pheniodol (B.P.C.).—Phenyl-hydroxy-diiodophenyl-propionic acid. A cream-white powder, insoluble in water. *Dose.*—3 to 6 G (45 to 90 gr.) in tablets or suspended in water.

USES

Pheniodol is a less toxic substitute for Iodophthalein and is often preferred as a contrast medium for radiography of the gall bladder. It is given twelve hours previously and fat-containing meals avoided until it may be desired to test the emptying of the gall bladder.

Iodoxylum.—Iodoxyl. Methyl-diiodo-pyridone-dicarboxylic acid. Uropac. Uroselectan-B.

CHARACTERS.—An odourless, white powder.—*Solubility.*—1 in 1·2 of water.

Dose.—*By intravenous injection:*

Metric, 10 to 15 G; Imperial, 150 to 225 gr.

Preparation

Injectio Iodoxyli.—A sterile (75%) solution in Water for Injection containing 0·75 G (12 gr.) in 1 Mil (15 min.) for intravenous injection.

ACTIONS AND USES

Iodoxyl is a diuretic during its rapid excretion by the kidneys. The Injection is given by slow (20 Mils in 5 minutes) intravenous injection, and radiograms of the kidneys are taken about 15 to 30 minutes after; but, in renal disease, the excretion is commonly delayed. The skin vessels may become dilated from the injection for a brief period. A 20 per cent. solution is used for retrograde pyelography, 10 Mils being injected.

Injectio Diodoni.—A sterile aqueous solution of the diethanolamine salt of Diiodo-pyridone acetic acid. Per-Abrodil. A colourless liquid.

Dose.—*By intravenous injection:*

Adult: **Metric, 20 Mils; Imperial, 300 min.**
Child: **Metric, 8 to 10 Mils; Imperial, 120 to 150 min.**
Infant: **Metric, 2 to 3 Mils; Imperial, 30 to 45 min.**

ACTIONS AND USES

Injection of Diodone is less irritant than that of Iodoxyl and can be injected intravenously a little more quickly. It is used like Iodoxyl for intravenous and retrograde pyelography, as well as for arteriography. Sudden circulatory collapse has occasionally happened from its use.

Oleum Iodisatum.—Iodized Oil. "Lipiodol." "Iodatol."

An Iodine addition product of poppy-seed oil; contains 40% Iodine.

CHARACTERS.—A pale-yellow oily liquid; odour alliaceous, taste bland. Sp. Gr. 1·340.

ACTIONS AND USES

Oleum Iodisatum is introduced in appropriate amounts into the bronchioles (20 c.c.), the urethra, uterine cavity and Fallopian tubes and into sinuses, in order to render these opaque to X-rays and to facilitate the location and diagnosis of disease and new growths.

Intraspinal injections of preparations with a lower specific gravity (10 per cent. Iodine), in dose of 5 c.c. emulsified in 5 c.c. of cerebro-spinal fluid, are used to assist the location of spinal and cerebral tumours; such injections may cause transient headache, febrile reaction, and dorsal stiffness or pain.

Iodoformum.—Iodoform. CHI_3.

CHARACTERS.—Small, shining, lemon-yellow, hexagonal crystals; odour and taste persistent, disagreeable. *Solubility.*—Very slightly in water; easily in fixed and volatile oils.

Preparations

Suppositoria Iodoformi.—Iodoform Suppositories. 0·2 G (3 gr.) in each with Oil of Theobroma.

ACTIONS AND USES

Iodoform is a weak **antiseptic**; it is said to be decomposed slowly by alkaline secretions and the tissues with the liberation of small amounts of Iodine.

It is used as an antiseptic for ulcers and superficial lesions, but it has no specific toxicity towards organisms. As a dressing for wounds, it is a protective which limits bacterial growth, and stimulates phagocytosis as well as granulation; further it has a slight **local anæsthetic** action which allays pain in the wound. It is used chiefly as a powder for dredging on the surface of wounds or as Iodoform gauze (5 to 20 per cent.).

Bismuth and Iodoform Paste ("Bipp") was used for wounds (see p. 66). Pigmentum Iodoformi Co. (B.P.C.) or Whitehead's Varnish, containing Iodoform with Benzoin, Storax and Tolu Balsam in Ether, is used to seal surgical wounds and to fix radium applicators.

The persistent odour of Iodoform renders it unwelcome to patients. Occasionally, Iodoform has caused erythematous or eczematous eruptions, or narcotic effects from its absorption from wounds.

BROMUM. BROMINE. Br. 79·92

The Bromide ion is employed mainly for its specific *depressant* action on motor nerve cells.

1. **Potassii Bromidum.**—Potassium Bromide. KBr.

   CHARACTERS.—Colourless, cubical crystals, or powder; odourless; taste saline. *Solubility.*—1 in 2 of water. *Incompatible* with *mineral* acids, Mercury and Silver salts, Strychnine and Sweet Spirit of Nitre.

   Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

   Preparation

   Tabellæ Potassii Bromidi.—0·3 G (5 gr.) in each.

2. **Sodii Bromidum.**—Sodium Bromide. NaBr.

   CHARACTERS.—Small, white, cubic crystals, somewhat deliquescent; inodorous; taste, saline. *Solubility.*—1 in 1·5 of water. *Incompatibles* as of Potassium Bromide.

   Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

   Preparation

   Tabellæ Sodii Bromidi.—0·3 G (5 gr.) in each.

ACTIONS AND USES

The saline taste of the Bromides excites a reflex secretion of saliva. In the stomach they act like neutral salts and, in large doses, may cause nausea and vomiting owing to irritation by the "hypertonic salt"; therefore, they should be given in dilute aqueous solution.

The Bromides are absorbed rapidly from the small intestine into the circulation and permeate all tissues of the body, where, in proportion to their relative intake, they displace Chlorides and perform the osmotic functions of these. The only tissues which are influenced by the substitution of the Bromide for the Chloride ion are nerve cells and upon these Bromides exert a specific depressant effect. This action does not result from displacement of Chloride ions, because the depressant effect of Bromides occurs before there is comparable substitution of Chlorides in the tissues and, as the percentage of Bromides remains higher in the blood than in nervous tissue, the latter has evidently no selective affinity for Bromide ions. Further, since Bromates and organic compounds, which do not liberate Bromide ions, do not have similar actions, it is clear that the depression is due to a specific influence of the Bromide ion on the nerve cells.

The action of Bromides commences with **depression of the higher psychical functions** of the brain and results in impaired attention and power of concentration, mental apathy, forgetfulness, and some confusion of thought and speech. Then, owing to **diminished excitability of the cerebral motor area**, there is induced a feeling of lassitude, fatigue and muscular weakness. The patient exhibits less interest in his surroundings and this apathetic mental state conduces to sleep but, as the perceptive and sensory centres are not influenced, the patient is easily roused by an external stimulus although remaining dull and confused. Since the sensory area is not depressed, Bromides do not relieve pain. The chief cerebral action of Bromides appears, from the lengthened reaction time, to be a depression of the association neurons connecting the perceptive centres with the intellectual and motor areas.

Large doses cause depression of the reflex centres in the medulla so that the pharyngeal and vomiting reflexes may be diminished or lost and respiration may be slower and weaker. Large continued doses of Bromides diminish the spinal reflexes but without abolishing sensation or perception of pain. Their activity in small doses in depressing sexual excitability is probably more a result of depression of cerebral associations than a direct action on the spinal centres.

Bromides have no other direct actions in the body; they do not influence the circulatory system, and the impression that Potassium Bromide depresses heart muscle is incorrect because the Potassium ion is rapidly excreted. The subnormal temperature of patients under the influence of Bromides results from decreased motor activity.

The therapeutic value of Bromides is dependent upon their power to retard the association of perceptive impressions and to depress the motor cortex. Sodium and Potassium Bromides are both effective and suitable for therapeutic purposes; the former has, however, a less objectionable taste and is less irritant to the stomach. Their value as **sedatives and hypnotics** is confined to cases where sleeplessness results from mental strain, worry, emotional or intellectual excitement and restlessness. In such conditions they may be given an hour or two before bedtime or in combination with Chloral Hydrate or other hypnotics. They are often useful also to allay restlessness and permit sleep during acute fevers and to give relief from nervous palpitation. It must be clearly understood that the Bromides are neither reliable nor rapid hypnotics and are of no value if pain be present.

The sedative influence of Bromides is used in **epilepsy**, where they lessen the frequency and severity of the convulsions; in some cases they effect a complete remission, but usually attacks return if the Bromide be discontinued. The object must, therefore, be to maintain that concentration of Bromides in the tissues which will avert attacks. This is achieved by commencing with doses of 2 G (30 gr.) daily and increasing by 0·3 G (5 gr.) daily in subsequent weeks until convulsive seizures are checked; the dose is then lowered to that which is adequate for the case. In practice, it is advisable to promote retention of the Bromide in the tissues by reducing the Chlorides in the patient's diet, but mental apathy and bromism are a common sequel; and for that reason Phenobarbitone, Phemitone, or Phenytoin is now preferred.

Bromides have a less reliable value in the treatment of hysteria and neurasthenia, or hyperthyroid excitement. They are often of service in relieving symptoms of reflex nervous origin, e.g. seasickness, the vomiting of pregnancy, nervous cough and persistent hiccough.

Bromides as antidotes for the convulsions of tetanus and Strychnine poisoning are of little use.

Bromides relieve the cerebral symptoms produced by overdosage with Quinine.

Excretion of Bromides.—The excretion of Bromides commences rapidly in the urine but, as the kidneys do not distinguish Chlorides from Bromides, the amounts eliminated will depend upon the proportion in the tissues and the excretion will continue slowly in gradually decreasing amounts for over a fortnight. If the Chlorides in the diet be reduced, Bromide excretion is diminished and, conversely, excess of Chlorides leads to more rapid excretion of Bromides.

Bromism.—This term is applied to the symptoms which arise from prolonged dosage with Bromides. The mental faculties are dulled and memory is impaired; the patient is in a state of lethargy; the pharyngeal reflex is absent and loss of appetite or indigestion is a common symptom; frequently (as in iodism) the mucous secretions of the nose and bronchi are increased. The predominant symptom, however, is a skin eruption, resembling acne, most common on the face, although it may spread to other parts of the body; the acneiform pustules may unite to form small abscesses or even ulcers. Occasionally the eruption is of an erythematous character. These eruptions may be diminished or prevented by administering Liquor Arsenicalis along with the Bromides, or the salt intake may be increased so as to accelerate the excretion of the Bromide.

GROUP II.—THE ACIDS

The British Pharmacopœia contains both inorganic and organic acids; many of the latter have important special actions, and are discussed in appropriate places.

INORGANIC ACIDS

1. **Acidum Hydrochloricum.**—Hydrochloric Acid. HCl. Hydrogen Chloride, 35% by weight, dissolved in water.

CHARACTERS.—A colourless, strongly acid, fuming liquid.

Preparation

Acidum Hydrochloricum Dilutum.—Dilute Hydrochloric Acid. Contains 10% of HCl.
Dose.—Metric, 0·6 to 8 Mils; Imperial, 10 to 120 min.

2. **Acidum Nitricum.**—Nitric Acid. HNO_3. Hydrogen Nitrate, 70% by weight, in water.

CHARACTERS.—A colourless, intensely acid, fuming liquid.

3. **Acidum Phosphoricum.**—Phosphoric Acid. H_3PO_4. Hydrogen Orthophosphate, 89% by weight, dissolved in water.

CHARACTERS.—A colourless, syrupy, acid liquid.

Preparation

Acidum Phosphoricum Dilutum.—Dilute Phosphoric Acid. Contains 10% of H_3PO_4.
Dose.—Metric, 0·3 to 4 Mils; Imperial, 5 to 60 min.

4. **Acidum Hypophosphorosum Dilutum.**—Dilute Hypophosphorous Acid. H_3PO_2. Contains 10% of H_3PO_2.

CHARACTERS.—A colourless, odourless, acid liquid.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

ACTIONS AND USES

Externally.—Concentrated acids, if applied to the skin, are **irritants** and **caustics**; they cause necrosis of the epidermis by extracting water from the cells, neutralizing their alkalinity and precipitating their proteins. After penetrating the superficial layers they irritate the sensory endings and cause intense pain which, if a large area be involved, may cause collapse. Acids are, however, less likely than alkalis to penetrate deeply because they are neutralized by the alkalinity of the tissues.

The caustic effect of individual acids differs. Sulphuric Acid (*not official*) chars the tissues, producing black scars. Hydrochloric Acid, being volatile, tends to spread and produce blistering around the area; the scar is white from protein precipitation. Both Sulphuric and Hydrochloric Acids tend to redissolve the precipitated proteins as acid meta-proteins and therefore tend to penetrate. Nitric Acid stains the tissues yellow but, as it does not readily redissolve the precipitated proteins, its action is more circumscribed.

For their caustic properties, Inorganic Acids are occasionally used to destroy warts, condylomata and external growths of benign nature. Concentrated Nitric Acid is the most satisfactory, but it should be applied only in small amounts, repeated if necessary.

Dilute Acids are antiseptics, but unsuitable for use as such.

Internally.—Strong Acids, if swallowed accidentally, produce deep corrosion of the mucous membrane of the mouth, throat and stomach.

In the *mouth*, Dilute Inorganic Acids stimulate the taste buds and reflexly augment salivary and gastric secretion and arouse appetite. By precipitating protein they have a slight astringent action upon the buccal mucous membrane but they are inadvisable for this purpose because they attack the teeth, to protect which they should be taken through a tube.

In the *stomach*, the administration of Dilute Acids in the dosage and dilutions commonly prescribed before meals increases gastric secretion; this effect is partly a reflex from the taste buds. Strengths above 0·5 per cent. inhibit the secretion for a time but these effects are not of therapeutic importance.

Given after meals, Dilute Acids supplement the acid present in the stomach, but the effect may be temporary only, because, by duodenal regurgitation of alkaline chyme, the normal degree of acidity is restored. The presence of 0·2 per cent. Hydrochloric

Acid in the stomach is **essential for peptic digestion**; the acid also assists the solution of connective tissue and acts as an **antiseptic.** The natural acid should be prescribed when it is deficient. The administration of Dilute Hydrochloric Acid during and after meals is invaluable in the **hypochlorhydria and achlorhydria** of chronic gastric catarrh and carcinoma as well as in that of pernicious anæmia and rheumatoid arthritis. In such cases doses of 60 min. are given diluted in 3 fl. ozs. (0·4 per cent.) or 6 fl. ozs. (0·2 per cent.) as an acid drink flavoured with orange or lemon juice and, if desired, along with pepsin. The administration of Dilute Acids is of value also in the diarrhœas of infancy and of adults due to bacterial enteritis arising from defective antiseptic action by the Hydrochloric Acid of the stomach.

The tone of the pyloric sphincter does not depend, as was supposed, on gastric acidity and, if the gastric acidity becomes high, an alkaline reflex from the duodenum takes place so as to lower the acidity. Acids excite a watery pancreatic secretion through the agency of secretin.

Dilute Nitric and Nitrohydrochloric Acids were formerly prescribed as cholagogues for "bilious" attacks; their value was due to replacement of the deficient acid in chronic gastric catarrh. Phosphoric Acid acts like other inorganic acids and has none of the actions of Phosphorus; Dilute Hypophosphorous Acid is not, although reputed to be, a nervine "tonic."

Actions after Absorption.—Acids are converted, by uniting with basic salts in the duodenum, into neutral or acid salts, and in this form are absorbed. The acid salts are neutralized either (*a*) by the buffer salts, e.g. $NaHCO_3$, of the plasma, the carbon dioxide evolved being excreted by the lungs or, (*b*) in carnivorous animals, by the formation of ammonia which acts as a protective against acids. Thus, in small therapeutic doses, Dilute Inorganic Acids do not materially reduce the alkali reserve of the blood nor increase considerably the urinary acidity; also, a change in the reaction of the blood towards the acid side increases renal filtration to rid the body of the unwanted acid salt.

Excretion of Inorganic Acids.—The excretion of Inorganic Acids as neutral or acid salts produces only slight diuresis, because their initial doses are small and they are of less value to increase the acidity of the urine than Ammonium or Calcium Chloride, or acid salts, e.g. Acid Sodium Phosphate.

5. Chromii Trioxidum.—Acidum Chromicum. Chromic Acid. CrO_3. (*Not official.*)

CHARACTERS.—Crimson needles, very deliquescent, corrosive. *Solubility*.—Readily in water. May explode with Glycerin, Ether, or Alcohol. *Incompatible* with most organic matter.

ACTIONS AND USES

Chromic Acid is a powerful oxidizing agent and thus a **caustic,** antiseptic and deodorant. As a caustic, a 10 or 20 per cent. solution in water may be used for warts, condylomata, granulations and indolent ulcers, etc. To restrict its surface action the skin may be protected by Soft Paraffin. Solutions of 2 to 3 per cent. strengths are useful **antiseptics** for hyperidrosis (sweating feet) and for ulcers and papillomata of the mouth, pharynx and nose. Solutions of 5 or 10 per cent. are used as paints for anaerobic organisms in the mouth, e.g. Vincent's infection.

ORGANIC ACIDS

1. **Acidum Aceticum Glaciale.**—Glacial Acetic Acid. $CH_3.COOH$. Hydrogen Acetate 99% with water.

CHARACTERS.—A clear, colourless acid liquid, with a very pungent odour. Crystallizes below 14·7° C.

2. **Acidum Aceticum.**—Acetic Acid. $CH_3.COOH$. Hydrogen Acetate, 33% by weight in water.

CHARACTERS.—A clear, colourless liquid, with a pungent odour and taste; reaction, strongly acid.

Preparations

1. **Acidum Aceticum Dilutum.**—Dilute Acetic Acid. Contains 6% of Hydrogen Acetate.
2. **Oxymel.**—Acetic Acid 15%, in Water and Purified Honey.

Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.

3. **Acidum Citricum.**—Citric Acid. Hydrogen Citrate $COOH.C(OH)(CH_2.COOH)_2,H_2O$.

CHARACTERS.—Large, colourless prisms, or white powder, with an acid taste. *Solubility*.—2 in 1 of water. 35 gr. in 1 fl. oz. of water, or 8%, makes a solution resembling lemon juice in acidity; 10 parts neutralize 14·25 parts of Potassium Bicarbonate, and 12 of Sodium Bicarbonate.

Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

4. **Acidum Tartaricum.**—Tartaric Acid. Dextro-rotatory Hydrogen Tartrate. $(CHOH.COOH)_2$.

CHARACTERS.—Colourless monoclinic prisms, or white powder with a strongly acid taste. *Solubility*.—1 in less than 1 part of water. 10 parts neutralize 13·25 parts of Potassium Bicarbonate, and 11·25 of Sodium Bicarbonate.

Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

ACTIONS AND USES

Externally.—Glacial Acetic Acid is a painful **caustic** and, being volatile, it penetrates and extends beyond the area of application; it is occasionally used to remove corns and warts. Acetic Acid, by penetration of the skin, irritates the sensory nerve endings and acts as a **rubefacient**, producing a sensation of heat and hyperæmia in the area of application. It is employed as a counter-irritant, usually in association with Turpentine as a liniment for sprains, myalgias, and subacute synovitis. Citric and Tartaric Acids have no external actions.

Internally.—Acetic, Citric and Tartaric Acids, by stimulating the taste buds, reflexly increase salivary secretion, and in the *mouth* they are useful **means of relieving thirst** in febrile patients. For this purpose a solution of 0·5 to 1 per cent. Citric Acid is most acceptable, or Lemon Juice (8 per cent. Citric Acid) may be ordered and diluted to taste.

In the *stomach* these organic acids have no important therapeutic value, but their excessive use interferes with digestion, and this explains the use of vinegar by the laity to reduce obesity. In the **duodenum** these acids are converted into Acetates, Citrates and Tartrates by the alkali of the intestinal secretions. These salts will raise the osmotic tension of the intestinal contents and to a slight extent prevent the absorption of water, but the acids are administered in too small doses for their salts to be effective saline purgatives. On the other hand when Tartaric and Citric Acids are given with Sodium Bicarbonate as effervescing preparations, the Tartrates and Citrates so formed are **useful saline purgatives,** and this principle is utilized in the Pulvis Effervescens Compositus (Seidlitz Powder).

From the intestine Acetates, Citrates and Tartrates are absorbed and are oxidized by the tissues into **bicarbonates.** These salts therefore produce an **increase in the alkali reserve** of the plasma (*see* p. 42). The bicarbonates are ultimately excreted by the kidney, and **the urine is rendered less acid** or even alkaline, but, if it is desired to produce this effect without disturbing digestion, Citrates or Tartrates, which can be given in larger doses, should be prescribed rather than the acids.

5. **Acidum Trichloraceticum.**—Trichloracetic Acid. $CCl_3.COOH$.

CHARACTERS.—Colourless deliquescent crystals; odour pungent. *Solubility.*—Readily in water, alcohol 90%, and ether.

ACTIONS AND USES

Trichloracetic Acid is a rapid and useful **caustic and antiseptic**; it is less painful than the mineral acids and is more suitable for mucous membranes. To remove warts, scars, and external growths, the pure Acid is employed. For ulcerating surfaces and leprosy, strengths of 1 in 3 or 5 of water are employed. In the mouth it is advantageous as an antiseptic caustic for pyorrhœal pockets, buccal ulcers, and tonsillar crypts. About 1 c.c. of a solution in an equal amount of Glycerin is used successfully as a caustic for growths in the bladder; guided by the cystoscope, the fluid is injected through a catheter.

6. Acidum Lacticum.—Lactic Acid. $CH_3.CHOH.COOH$. An aqueous liquid containing *75% of Hydrogen Lactate with 10% of Lactide,* $C_6H_8O_4$.

CHARACTERS.—A colourless, hygroscopic, syrupy liquid; inodorous; taste sour. Miscible in all proportions with water, alcohol 90%, and ether.

Injectio Sodii Lactatis Composita.—Ringer-Lactate Solution. Hartmann's Solution (*see* p. 43).

ACTIONS AND USES

Externally.—Lactic Acid is a good **caustic and antiseptic** for mucous membranes, because it has a low toxicity. In the mouth it is valuable for gingivitis and aphthous ulceration; it is also employed to cauterize tuberculous ulcers of the pharynx or larynx and, diluted, to remove diphtheritic membrane.

Internally.—Milk soured by adding Lactic Acid (45 min. per pint) gradually while stirring, or dried Lactic Acid Milks diluted with water, are used as feeds in the gastro-enteritis of infants, in order to check the vomiting and diarrhœa.

Ringer-Lactate Solution (Hartmann's Solution) is given intravenously to treat ketosis in diabetic coma and infantile gastro-enteritis; the Sodium Lactate becomes slowly converted to Sodium Bicarbonate without inducing alkalæmia (*see* p. 43).

GROUP III.—WATER, OXYGEN AND CARBON DIOXIDE

Aqua Destillata.—Distilled Water. H_2O. Pure Water prepared by distillation from potable Water.

Aqua Pro Injectione.—Water for Injection. Potable Water distilled from a neutral glass or metal still which prevents entrainment. The distillate is suitably sealed to exclude bacteria and sterilized at once in an autoclave. If required free from carbon dioxide the distillate is boiled for 10 minutes prior to sealing and sterilizing. Water for Injection must comply with tests for sterility and freedom from pyrogens, and, if sealed by a cotton-wool plug, must be used within a month of preparation.

ACTIONS AND USES

Externally.—In the British Pharmacopœia, Distilled Water is employed as a solvent for various remedies. Water for Injection is used to prepare most of the official Injections and is the advisable solvent for all remedies which are to be given by hypodermic, intramuscular or intravenous injection, but large amounts will cause laking of erythrocytes; this is obviated by using sterile Normal Saline or Ringer's Solutions as the solvent.

Water is a means of applying heat or cold to the surface of the body. It is used in various types of **baths**, e.g. cold, tepid, warm, hot, vapour, or medicated, and also by sponging, douching, or fomenting. Sponging with tepid water or a cool bath (80° F.)—the skin being left damp—is a valuable resource for **lowering febrile temperature** temporarily and for promoting comfort and sleep. Hot baths are serviceable to promote free perspiration and to relieve pain, muscular spasms, convulsions, and delirium; they are also useful in insomnia (*see* p. 583).

Water is not absorbed by the normal skin; the epithelium imbibes water and swells, but the stratum corneum acts as a barrier to the absorption of water and substances dissolved in it. Hot Water, 43°–49° C. (110°–120° F.) is a useful **hæmostatic** for capillary bleeding and, as a uterine douche, for post-partum hæmorrhage.

Internally.—Water is contained in all natural foods and beverages. It relieves thirst and checks hunger contractions in the stomach. Taken with meals it prolongs the action of the salivary enzymes and increases the secretion of both pepsin and acid in the gastric juice. Water is absorbed only to a slight extent from the stomach; it passes quickly into the bowel where absorption occurs rapidly in the small, and more slowly in the large, intestine.

After absorption, Water temporarily makes the plasma more hydræmic and lowers its osmotic tension, but the surplus water is quickly absorbed by the tissues—especially by the muscles and skin. A constant **balance of salts and water** in the plasma is maintained by the combined actions of the antidiuretic pituitary hormone, Vasopressin, and of the cortical hormone of the suprarenals; the former being influenced by a hypothalamic centre.

Water is the **natural diuretic measure**; it is indicated when it is desirable to flush the glomeruli and tubules free from blood, pus, cellular débris or relatively insoluble excretory substances. When a draught of water is taken, the amount of urine flow begins to increase in 15 to 30 minutes, is maximal in about 2 hours, and is again normal after about 4 hours. Aeration with Carbon Dioxide or the addition of dilute Alcohol increases the rapidity with which water is absorbed and excreted, so that these or more active diuretics may be employed to increase the speed and degree of its action. Water diuresis results in the production of a very dilute urine, but the daily excretion of the solid urinary constituents is also increased; therefore water is therapeutically useful, not only to reduce irritation in inflammatory conditions of the urinary passages, but also to facilitate the removal in solution of waste products and of drugs. Diuresis and perspiration are vicarious functions, for in a warm atmosphere excretion by the sweat glands will predominate over diuresis, and *vice versa*.

In order to **promote diaphoresis** in fevers, Water is best given in the form of hot milk, soup, gruel, or hot drinks containing alcohol. The principle of withholding fluids in febrile conditions is irrational.

Oxygenium.—Oxygen. O. 16·00.

CHARACTERS.—A colourless, odourless gas; prepared by the fractional liquefaction of liquid air or by electrolysis of water. Supplied compressed in metal cylinders, which are painted *black* with the shoulder *white*, the name of the gas painted or indelibly stamped on the body, and the name or symbol on the shoulder and valve; the connecting tubing should be *white*. Air contains 20% Oxygen.
Dose (*not official*).—**3 to 6 litres per minute, by inhalation.**

Oxygen and Carbon Dioxide Mixtures, usually 95% O_2 with 5% CO_2, are supplied in cylinders which have the body painted *black* and the shoulder *sea-green* with a *white* neck, the name of the gas painted or indelibly stamped on the body and the formula on the *white* neck in *black* lettering.

ACTIONS AND USES

The Oxygen necessary for the tissues is obtained from that in free solution in the plasma, which derives a supply adequate to the varying needs of the tissues from the Oxygen in loose chemical combination with the hæmoglobin of the corpuscles. The dissociation curve of hæmoglobin is so designed that it increases rapidly with decrease in the Oxygen tension of its surroundings, so that the blood can liberate Oxygen in amounts appropriate to the variable requirements of different tissues. Any increase, due to augmented tissue metabolism, in the production of Carbonic or Lactic Acids also increases the dissociation of Oxygen from oxyhæmoglobin, and this further ensures an adequate supply of Oxygen from the blood to active tissues.

When air is breathed, the arterial blood becomes almost fully (95 per cent.) saturated with Oxygen; it takes up 18·2 per cent. in combination with hæmoglobin and 0·3 per cent. in solution by the plasma. Even if pure Oxygen is breathed, the oxyhæmoglobin can take up only about 0·2 per cent. more, but the **Oxygen dissolved in the plasma increases** in proportion to the oxygen tension in the alveolar air and the amount in solution in the plasma can, therefore, increase from 0·3 to as much as 3 per cent. Upon this fact the value of Oxygen inhalations depends.

When the tissues receive insufficient supplies of Oxygen, **anoxia** or **anoxæmia** results. This may arise from: (1) defective saturation of the blood with Oxygen (anoxic type), in which the pressure of Oxygen in the blood is too low; this occurs in rarefied atmospheres or from decreased pulmonary ventilation due to partial consolidation (pneumonia, pulmonary œdema or effusion), drowning, suffocation, etc., or mucus in the air cells; (2) deficiency of hæmoglobin (anæmic type), arising in chlorosis and other anæmias, or from formation of carboxyhæmoglobin in carbon monoxide poisoning, or of methæmoglobin in poisoning by Nitrites, Acetanilide, etc.; (3) defective blood supply to the tissues (stagnant type), where the circulation is inefficient, as in cardiac failure or in hæmorrhage, shock, or syncope.

In mild degrees of anoxia, the chief symptoms are headache, giddiness, faintness and dyspnœa on exertion, associated with varying degrees of cyanosis of the "grey" type. There is an initial increase in respiration but this increase causes an excessive elimination of Carbon Dioxide; the consequent decrease in the Carbon Dioxide and the Hydrogen ion concentration in the blood depresses the respiratory centre; the breathing therefore becomes rapid and shallow, or even quiescent. The decrease in the H-ion concentration of the blood so alters the Oxygen dissociation curve from the normal that less Oxygen dissociates at a given tension to become available for the tissues. Thus the tissues are deprived of Oxygen in two ways, and a mild degree of anoxia may become progressively worse, hence cyanosis or symptoms of discomfort may be absent although the patient is suffering from lack of Oxygen.

In severe anoxia, breathing is rapid but shallow and often periodic (Cheyne-Stokes respiration), the pulse is rapid and the blood-pressure slightly raised, the mental faculties are dull, memory is impaired, and cyanosis is a prominent symptom.

Oxygen Inhalations.—The Oxygen released from the cylinder is conveyed through a rubber bag and is then warmed by allowing it to bubble through warm water in a Woulff's bottle. To increase the plasma Oxygen, the alveolar Oxygen must be raised from 14 to 40 per cent. For inhalation, an inverted filter funnel is a wasteful emergency. An Oxygen tent is useful for children. With a nasal catheter, 6 litres per minute gives an alveolar air concentration of 45 per cent. More efficient and acceptable by patients is a B.L.B. mask, with which 3 litres per minute gives 46 per cent. in the alveolar air.

The flow is adjusted between 3 to 6 litres per minute by regulating the speed of the bubbles in the Woulff's bottle, and is modified in accordance with the symptomatic relief obtained. Concentrations of 95 to 100 per cent. Oxygen afford prompt relief, but, except in high altitudes, cannot be given for long periods; the usual percentage is 50 at sea-level and over 60 per cent. should be used only if this fails to relieve the anoxia. Commonly, it is given with 5 per cent. of Carbon Dioxide. The administration should not be interrupted until the emergency has passed.

Therapeutic Applications.—The essential value of Oxygen in treatment is in the anoxic and anæmic types, where the blood is inefficiently oxygenated. Oxygen inhalations are of great assistance **in pneumonia** and broncho-pneumonia, in which they relieve dyspnœa and cyanosis and slow the pulse-rate; they should be commenced as soon as symptoms of anoxia develop and before cyanosis is apparent. Inhalations are also beneficial in emphysema and asthma, and in pulmonary œdemas resulting from the inhalation of irritant gases.

In **poisoning** by Morphine, Cyanides or Carbon Monoxide, and by drugs which form methæmoglobin, e.g. Chlorates, Acetanilide, Nitrites, Sulphanilamide, etc., Oxygen inhalations will tide over an anoxic crisis and allow time for the blood to recover its functions. Simultaneous inhalation of Carbon Dioxide is also advisable to stimulate the respiratory centre.

In the stagnant type of anoxia occurring in advanced cardiac disease, Oxygen is not often beneficial, because there is adequate aeration of the lungs and the anoxia arises in the tissues owing to the slow circulation; but it sometimes improves the condition of the patient by ensuring better oxygenation of the heart muscle.

Carbonei Dioxidum.—Carbon Dioxide. CO_2.

CHARACTERS.—A heavy, colourless, odourless gas, prepared from mineral carbonates or by fermenting sugar. In aqueous solution its taste is faintly acid. Supplied compressed in metal cylinders, which have the shoulder and upper 3/4 of the body painted *sea-green* and the lower 1/4 *black*, the name of the gas painted or indelibly stamped on the body with the name or formula on the shoulder and valve; the connecting tubing should be *sea-green*.

Dose (*not official*).—**From 1 to 5% diluted with Oxygen or air, by inhalation.**

Carbon Dioxide for "Snow" Making is in cylinders with an internal tube, the whole cylinder being painted *sea-green*.

ACTIONS AND USES

Externally.—Carbon Dioxide, in the form of natural or artificial **effervescing baths,** acts as a **mild stimulant** to the skin. Such baths dilate cutaneous vessels, and lower blood-pressure; they are used in the "Nauheim" treatment of cardiac failure. The inhalation of the gas, which stimulates respiration, contributes to the beneficial effect.

Solidified Carbon Dioxide in pencil form is used as a **caustic** to destroy, by freezing, warts, nævi, lupus and rodent ulcers; the pencil is applied for from 5 to 40 seconds, according to the size of the growth. The method—termed "refrigeration" or "crymotherapy"—is almost painless, and the resulting scars are pale, soft and pliable.

Internally.—Carbonic Acid, evolved in effervescing preparations, or as the result of administering Bicarbonates or Carbonates, acts as a **stimulant to the gastric mucous membrane,** increasing its vascularity and augmenting the gastric secretion, especially the acid. For this reason Bicarbonates and Carbonates are less useful in treating hyperacidity than Oxides and Hydroxides.

Carbon Dioxide also increases the movements of the stomach, accelerates the passage of food into the intestine, and increases the rate of intestinal absorption, especially of water. For this last reason "Soda Water" is a rapid means of relieving thirst and promoting diuresis.

Inhalation of Carbon Dioxide.—Carbon Dioxide is the normal stimulant and regulator of the respiratory centre in the medulla and it is also the chief acid controlling the acid-base balance of the blood and tissues. Normally the atmospheric air contains about 0·04 per cent. and the alveolar air about 5·6 per cent. of Carbon Dioxide. Any increase in the amount of Carbon Dioxide in the inspired air leads to increased Carbon Dioxide tension in the arterial blood, with consequent stimulation of respiration to promote removal of the excess of the gas.

It is known that 3 per cent. of Carbon Dioxide in the inspired air will double the depth of respiration, and 5 per cent. will treble it and also increase the frequency per minute. Strengths of 6 to 8 per cent. produce headache, mental confusion, obvious dyspnœa with rise of blood-pressure and slow pulse from stimulation of the vaso-motor and vagal medullary centres, as well as cyanosis of a "blue" type, because such percentages are above that normally present in alveolar air and, when they are inhaled, the increased breathing cannot reduce the alveolar percentage to normal.

Therapeutic Applications.—Inhalation of Carbon Dioxide is a rapid and effective means of **stimulating the respiratory centre** and of increasing particularly the depth of respiration. Usually it is employed as a mixture of 5 per cent. Carbon Dioxide in 95 per cent. of Oxygen; the mixture is available in cylinders, or may be prepared from cylinders of the separate gases in a rubber bag, and is inhaled from a mask provided with suitable valves.

The combined gases have been used successfully to arouse respiration in the new-born, in drowning, in poisoning by Morphine, general anæsthetics, organic hypnotics, and Carbon Monoxide. In empyema they are also of service to cause increased expansion of the lung.

Carbon Dioxide inhalations have been used to promote deep respiration and accelerate absorption of Ether by the blood for anæsthetic purposes, and again, after operations, to hasten excretion of anæsthetic vapours, to accelerate the return of consciousness, and to minimize the risk of post-operative nausea and bronchitis.

It should be noted that during anæsthesia deep respiration may cause excessive excretion of Carbon Dioxide and consequently a reduced stimulus to the centre, which is already partly depressed by the anæsthetic; from these two causes, respiratory failure may occur during anæsthesia with the tissues in a state of anoxia as well as acapnia.

PART II

THE VEGETABLE AND ANIMAL MATERIA MEDICA AND SYNTHETIC PREPARATIONS

DRUGS USED MAINLY FOR THEIR ACTION ON THE DIGESTIVE SYSTEM

THE drugs which produce their chief effects on or through the digestive system will be arranged in groups according to their actions and uses.

I.—COLOURING AGENTS

Colouring Agents are employed in pharmacy to render the appearance of mixtures more acceptable or to disguise the other ingredients. They serve also to distinguish solutions of colourless poisons; thus Mercuric Chloride Solution is often tinted with methyl violet, the Biniodide with eosin, and Mercury-Zinc Cyanide with aniline violet, when they are dispensed as antiseptics. One Colouring Agent is official.

Coccus.—Cochineal. The dried female insect, Dactylopius coccus, containing eggs and larvæ. N.O. Hemiptera.

CHARACTERS.—An oval, purplish-black insect about 5 mm. long; when powdered it is dark red.

COMPOSITION.—*Carmine* or *carminic acid,* red-coloured crystals, readily soluble in water and alcohol.

Preparation

Tinctura Cocci.—10% in Alcohol 45%.

ACTIONS AND USES

Cochineal is used as a **colouring material** only. The colour is changed to yellow by mineral acids and to purple by alkalis. Water containing lime salts may precipitate the Carmine.

Liquor Azorubri (B.P.C.).—Liquor Ruber. A 1% solution of Bordeaux B. This is a more satisfactory colouring agent as its red colour is not affected by acids or alkalis.

II.—DEMULCENTS

A demulcent is a drug of viscid character which protects mucous surfaces from irritation. The following drugs are demulcents: Acacia, Tragacantha, Mel Depuratum and Boracis, Glycyrrhiza, Gelatinum, Glycerinum, Amylum; and also bland Fixed Oils and Albumin.

Acacia.—Gum Acacia. A gummy exudation from the stem of Acacia senegal. N.O. Leguminosæ.

CHARACTERS.—Rounded or ovoid, yellowish, glistening tears or masses; taste bland and mucilaginous. *Solubility.*—Entirely soluble in water, yielding a faintly acid, viscous, colloidal solution. *Incompatible* with alcohol, borax, acids, ferric salts, lead subacetate.

COMPOSITION.—Gum Acacia consists of *arabic acid*, or *arabin*, united with calcium, magnesium and potassium; two sugars, *arabinose* and *galactose*; and water.

Preparations

1. **Mucilago Acaciæ.**—Gum 4 in Chloroform Water 6; recently prepared.
2. **Pulvis Tragacanthæ Compositus.**

ACTIONS AND USES

Externally.—Acacia is a cohesive and **protective** agent and is used—equal parts of the Mucilage and Glycerin—to suspend insoluble powders for application as pastes to the skin.

Internally.—Acacia is **demulcent**; it coats mucous surfaces with a gummy layer which protects them from irritation; therefore, the Mucilage is used as a vehicle for irritant drugs and as a basis in antiseptic pastilles for tonsillitis and pharyngitis. In the intestine, Acacia, by coating the mucous membrane, acts as a protective. The Powdered Gum and the Mucilage are used chiefly for the **emulsification** of oils and resins, for the **suspension** of insoluble powders and as **excipients** for making pills; the Mucilage is, however, apt to cause clumping of Bismuth salts (*see* pp. 17–18).

Intravenous injections of gum-saline solution (6 per cent. Acacia in Normal Saline), which has the same colloidal and saline osmotic tension as the blood, were formerly used to restore blood-volume and blood-pressure after severe hæmorrhage.

Tragacantha.—Tragacanth. A gummy exudation got by incising Astragalus gummifer. N.O. Leguminosæ.

CHARACTERS.—Thin, white or pale yellow, flat or curved, horny flakes with concentric ridges; inodorous; almost tasteless. *Solubility.*—Sparingly in water, but swells into a gelatinous mass.

COMPOSITION.—Tragacanth consists of two gums; *tragacanthin* (*bassorin*), a compound of bassoric acid, forming with water a colloidal gel; and a soluble gum, yielding geddic acid, arabinose and galactose.

Preparations

1. **Mucilago Tragacanthæ.**—Powdered Tragacanth 1·25% with Alcohol 90% and Chloroform Water.
2. **Pulvis Tragacanthæ Compositus.**—Powdered Tragacanth, 15; Gum Acacia, 20; Starch, 20; Sucrose, 45.

Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.

ACTIONS AND USES

Tragacanth has the same actions and uses as Acacia. It is more suitable for suspending Bismuth salts, but mixtures made with the Compound Powder are liable to fermentation. It is used as an adhesive for dentures, and with Glycerin to form pastes for treatment of skin diseases.

Gelatinum.—Gelatin. The protein extracted from collagenous material.

CHARACTERS.—Translucent, almost colourless sheets or shreds; tasteless. *Solubility.*—In cold water softens, swells and imbibes 5 to 10 times its weight of water; soluble in hot water and forms a gel on cooling; soluble in mixtures of Glycerin with water; insoluble in Alcohol 90%.

COMPOSITION.—Gelatin is a protein, *glutin*, which yields the amino-acid *lysine* but no tryptophane. Aqueous solutions are precipitated by tannic acid.

ACTIONS AND USES

Externally.—A paste of Gelatin, 18 per cent., in equal parts of Glycerin and Water forms an excellent **protective** and basis in which to incorporate antiseptics, e.g. Ichthammol, Resorcin, or astringents, e.g. Gelatinum Zinci, for the treatment of skin diseases.

Internally.—**Gelatin capsules** are a convenient means of giving unpleasant drugs. To prevent their solution in the stomach, they may be dipped in stearic acid, or keratin solution, or hardened in formalin (1 in 10).

Gelatin is a valuable **demulcent**, used chiefly in the form of pastilles, which are prepared from a basis containing Gelatin 12 per cent. and Glycerin 50, in Water (Glycogelatinum, B.P.C.). To this basis antiseptics or astringents may be added for the treatment of sore throat. Nasal, urethral and vaginal bougies are also made from the basis or with Suppositorium Glycerini.

Gelatin is easily digested and absorbed; having a high nitrogen content, it has some value as a **food** for invalids in the form of Calves' Foot Jelly, suitably flavoured.

Mel Depuratum.—Purified Honey. Honey of Commerce melted and strained.

CHARACTERS.—A syrupy liquid; odour aromatic; taste sweet.
COMPOSITION.—Honey is a complex mixture of several sugars, namely *dextrose*, *lævulose* and traces of *sucrose*, *dextrin*, and *proteins*; wax, pollen, colouring and odorous matters.

ACTIONS AND USES

Honey acts as a **demulcent**; and from its taste it increases slightly the secretion of saliva. It is used as a sweetening agent and as an ingredient of gargles, linctuses and cough mixtures. Internally, Honey is slightly **laxative** and is **nutritive**. It is contained in Oxymel and Oxymel Scillæ.

Glycyrrhiza.—Liquorice Root. The peeled root and subterranean stem of Glycyrrhiza glabra. N.O. Leguminosæ.

CHARACTERS.—Long, pale-yellow roots, with a thick bark, radiating bast fibres and calcium oxalate cells. Powder, pale yellow. Odour faint; taste sweet.
COMPOSITION.—Liquorice contains *glycyrrhizin* (*K and Ca salts of glycyrrhizinic acid*), *dextrose*, *starch*, *resin*, *asparagin* and *proteins*.

Preparations

1. **Extractum Glycyrrhizæ.**—A Soft Extract made with Chloroform Water.
Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.
2. **Extractum Glycyrrhizæ Liquidum.**—Made with Chloroform Water and Alcohol 90%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
3. **Pulvis Glycyrrhizæ Compositus.**—Compound Liquorice Powder. Liquorice, 16; Senna Leaf, 16; Fennel, 8; Sublimed Sulphur, 8; Sucrose, 52.
Dose.—Metric, 4 to 8 G; Imperial, 60 to 120 gr.

ACTIONS AND USES

Liquorice has a pleasant taste and, when slowly chewed, increases the flow of saliva. The powdered root is a useful **diluent** for compounding pills and the Liquid Extract **masks the tastes** of Senna, Aloes, Ammonium Chloride, Senega, Hyoscyamus, and Magnesium Sulphate. The extracts are popular **demulcents** and are used to mitigate sore throat and cough. The Compound Powder is a useful **laxative** for children.

Glycerin (*see* p. 389) is also a useful demulcent, and, in poisoning by corrosive acids or metallic salts, the bland fixed oils—

Olive and Almond Oils—or solutions of albumin—egg-white—are employed.

III.—FLAVOURING AGENTS AND CARMINATIVES—THE VOLATILE OIL SERIES

Flavouring Agents are aromatic substances used to impart an agreeable odour and taste to pharmaceutical preparations. They are selected according to the partiality of the patient and to the objectionable tastes which they serve to mask.

Carminatives are drugs, usually containing Volatile Oils, which assist the expulsion of gas from the stomach and intestines, and which thus relieve flatulence and colic.

Volatile Oils are both flavouring agents and carminatives.

Anethum.—Dill Fruit. The dried ripe fruit of Anethum graveolens. N.O. Umbelliferæ.

CHARACTERS.—The separate brown mericarps are oval and flattened, the edges forming pale-brown wings; each contains six oil glands. Odour and taste agreeably aromatic.

COMPOSITION.—Dill contains 3·5% of the *Volatile Oil.*

Oleum Anethi.—Oil of Dill. Distilled from the fruit.

CHARACTERS.—Colourless or pale yellow, darker on keeping; odour of the fruit; taste sweet, aromatic, later pungent.

COMPOSITION.—*Carvone*, $C_9H_{14}C = O$, 50%, a cyclic ketone; and terpenes, *d-limonene*, $C_{10}H_{16}$, and *phellandrene*, $C_{10}H_{16}$.

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

Preparation

Aqua Anethi Concentrata.—Oil of Dill 2% in Alcohol 90%, and Distilled Water. *Diluted with* 39 *parts of Water for use as an Aromatic Water.*

Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

ACTIONS AND USES OF VOLATILE OILS

Dill may be taken as a type of the preparations which owe their actions to the Volatile Oils contained in them. A description will therefore be given here of the general actions of Volatile Oils, with occasional qualifications referring to individual drugs. The aromatic Volatile Oils—ethereal or essential oils—vary in composition, but most consist of a fluid portion, termed elæoptene, which contains aromatic hydrocarbons of the terpene series $(C_5H_8)_n$. Most Volatile Oils contain oxidized aromatic bodies, termed stearoptenes, which, chemically, may be *alcohols*, e.g. Menthol, Citronellol; *aldehydes*, e.g. Citral, Cinnamic Aldehyde; *ketones*, e.g. Carvone, Fenchone; or *phenol-ethers*, e.g. Anethol, Eugenol, Myristicin; or a *phenol*, e.g. Thymol.

Externally.—Volatile Oils when applied to the skin act as **irritants.** Being volatile and soluble in fats, they penetrate easily, cause a sensation of warmth and smarting by irritating the sensory endings, and produce by an axon-reflex local vascular dilatation and redness. Soon the irritation is replaced by a mild local anæsthesia, due to subsequent paralysis of the sensory nerve endings. For these reasons certain of the Volatile Oils, such as Turpentine, Camphor, Thymol, Menthol and Methyl Salicylate, are used as **counter-irritants** and cutaneous stimulants in the treatment of chronic inflammatory swellings, synovitis and sprains, to relieve neuralgic and rheumatic pains, and as stimulant applications to the chest-wall in bronchitis, pleurisy, etc. (*see* pp. 432–438).

Volatile Oils are also **antiseptics.** Although their toxicity to the tissue cells is slight, they are, on account of their irritant action and insolubility in water, not often utilized as skin antiseptics. Turpentine can be used to disinfect the hands or instruments in emergency, and Menthol, Thymol and Eucalyptus Oil are occasionally employed as stimulant antiseptics for skin diseases.

Internally.—In the *mouth* the Volatile Oils are again irritant. If concentrated, they give rise to sensations of burning and heat; the mucous membrane becomes reddened, owing to vascular dilatation. In dilute solutions, they stimulate the nerves of taste and smell, and reflexly induce **salivation.** At the same time the stimulation of the olfactory and gustatory nerves by a pleasant Volatile Oil leads to a feeling of hunger and **increases the appetite** for food; reflexly a flow of **gastric juice is excited.** In other words, they **increase the desire for, enjoyment of, and digestion of food.** Aromatic Oils are accordingly used very extensively in cookery; and those which are associated with bitters, e.g. Orange, are taken as aperitives to stimulate appetite and digestion before a meal. For the same reasons, they are used in stomachic mixtures for atonic dyspepsia.

Volatile Oils are employed in pharmacy to impart an agreeable flavour to mixtures, etc., containing drugs with a nauseous or objectionable taste.

In the mouth, Volatile Oils are also **antiseptic,** and are used (1 to 3 per cent.) very largely for this purpose in tooth powders and pastes, when their stimulant and rubefacient action on the gums is a further advantage. Clove Oil is employed in **dentistry** to relieve pain from sensitive dentine and from exposed nerves in carious cavities; it is also an antiseptic for root canals.

In the *stomach* the Essential Oils are **mild irritants.** They cause a sense of heat in the epigastrium which arouses appetite, and they increase the vascularity of the mucous membrane. They act also as **carminatives** by reducing the tone and spasmodic contractions of an over-full stomach, and relax the cardiac sphincter, thus facilitating the oral expulsion of flatus. Further, by stimulation of the sensory endings they often excite the gastro-colic reflex and the expulsion of gas from the colon *per anum*. Their use in liqueurs after meals is familiar.

Reflex Effects.—By their irritation of the gastric mucous membrane, Volatile Oils, reflexly through the medulla, may cause some quickening of respiration, acceleration of the heart and rise in blood-pressure for a brief period. The cerebrum is also stimulated and attention aroused. They are, for this reason, given as **reflex restoratives** in syncope, along with more potent irritants, e.g. Spiritus Ammoniæ Aromaticus, and Spiritus Camphoræ. Valerian, owing to its persistent unpleasant taste which "repeats," is used as a reflex stimulant to the central nervous system in cases of hysteria and malingering. Volatile Oils are also **reflex expectorants** and this is the function of Camphor in Tinctura Opii Camphorata; further, they may be **reflex diaphoretics.**

In the *intestine*, Volatile Oils continue to act as **carminatives** by relaxing the muscular tone and diminishing spasmodic contractions due to local gaseous accumulations or to irritants, and thus they relieve flatulent colic and the griping tendencies of purgatives; for this reason they are contained in several official purgative preparations.

The mild stimulation of the Volatile Oils upon the intestinal mucosa increases its vascularity and absorptive powers. Their antiseptic action upon intestinal bacteria is of no therapeutic importance, but it possibly contributes to their value in reducing flatulence. In large doses their toxicity towards lower organisms renders certain Volatile Oils, e.g. Thymol, Turpentine, Chenopodium, valuable as **anthelmintics** to remove intestinal parasites (*see* p. 183). Such large doses are, however, apt, by irritation, to cause gastro-enteritis and diarrhœa.

Actions after Absorption.—The Volatile Oils are readily absorbed and circulate, chiefly unchanged, in the blood; to some extent terpenes are oxidized to terpenols.

In the kidneys Volatile Oils are excreted unchanged or combined with glycuronic acid. Owing to irritation of the renal epithelium, they produce **diuresis** and in large doses can cause nephritis. After excretion they act as **urinary antiseptics**, effective both in acid and alkaline urines; those formerly used were for this purpose Copaiba, Oil of Sandal Wood, and Buchu.

By a similar irritant action on the respiratory mucous membrane during their excretion, Volatile Oils stimulate the secretions of the bronchial glands and are mild **expectorants** and also **antiseptics**, but the amount excreted is too small to be actively toxic to bacteria. Inhalations of vaporized Volatile Oils, e.g. Oil of Eucalyptus, Oil of Pine, Terpene Hydrate, etc., are used to effect a direct antiseptic action on the bronchial mucous membrane in bronchitis.

Toxic Effects.—Absorption of large doses of Volatile Oils produces first a stimulation of the cerebrum, especially the motor area, and of the medulla with symptoms of motor excitement, delirium, and epileptiform convulsion along with rapid respiration, rise of blood-pressure and, commonly, a slow pulse; the pupils are dilated. Depression ensues later, causing narcosis or coma and failure of respiration. Skin eruptions commonly occur, and during recovery nephritis and hæmaturia must be avoided by giving fluid freely.

SPECIAL USES OF DILL

Oil of Dill and Dill Water have the actions of Volatile Oils; they are used very largely as **carminatives** to relieve griping in infants and children, and as flavours for saline purgative mixtures.

Oleum Menthæ Piperitæ.—Oil of Peppermint. The oil distilled from fresh-flowering peppermint, Mentha piperita. N.O. Labiatæ.

CHARACTERS.—Colourless or pale, greenish-yellow; odour characteristic; taste, pungent and aromatic, followed by a sensation of cold. COMPOSITION.—Not less than 46% of the alcohol, *menthol*, $C_{10}H_{19}OH$, and from 4 to 9% of esters as *menthyl acetate* $C_{10}H_{18}CH_3.COOH$; with *menthone*, *cineole*, *pinene*, *limonene*, etc.
Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

Preparations

1. **Aqua Menthæ Piperitæ Concentrata.**—Oil of Peppermint 2% in Alcohol 90% and Distilled Water. *Diluted with* 39 *parts of Water for use as an Aromatic Water.*
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.
2. **Emulsio Menthol Piperitæ.**—Oil of Peppermint 10%, emulsified by Quillaia Extract in Distilled Water.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.
3. **Spiritus Menthæ Piperitæ.**—Oil of Peppermint 10% in Alcohol 90%.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.

ACTIONS AND USES

The preparations of Peppermint are favourite flavouring agents with powerful **carminative** effects; they are used to relieve gastric and intestinal flatulence, colic and griping. If applied externally or used in the mouth, the Oil, or its solutions, owing to the presence of Menthol, cause at first slight irritation and then a sense of coldness and mild anæsthesia; the Oil is therefore used externally for the treatment of superficial neuralgias and muscular rheumatism (*see* Menthol, p. 436), and, as an ingredient of tooth pastes (1 to 3 per cent.), it imparts a pleasant cool sensation to the gums and is an antiseptic. The Spirit of Peppermint is an active carminative and reflex general stimulant.

Oleum Anisi.—Oil of Anise or Aniseed. The oil distilled from the dried fruit of Pimpinella Anisum, N.O. Umbelliferæ, or dried fruits of the star anise, Illicium verum, N.O. Magnoliaceæ.

CHARACTERS.—Colourless or pale yellow; odour of the fruit; taste sweet, aromatic. Crystallizes about 15° C.

COMPOSITION.—A phenol-ether, *anethole*, $C_9H_9OCH_3$, 80%; its isomer, *methyl chavicol*; a terpene, $C_{10}H_{16}$; and oxidation products.

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

ACTIONS AND USES

Anise is believed to exert, during its excretion, a special **expectorant** action on the bronchial mucous membrane. It is commonly used as the flavouring agent for cough mixtures and lozenges. It is contained in Tinctura Opii Camphorata.

Carum.—Caraway Fruit. The dried ripe fruit of Carum Carvi. N.O. Umbelliferæ.

CHARACTERS.—The separated brown mericarps are slightly curved and tapered. Each contains six oil glands. Odour and taste aromatic.

COMPOSITION.—The *Volatile Oil of Caraway* (3%).

Oleum Cari.—The oil distilled from Caraway Fruit.

CHARACTERS.—Colourless or pale yellow, with characteristic odour and taste.

COMPOSITION.—*Carvone*, $C_9H_{14}C = O$, a cyclic ketone, and *carvene* or *d*-limonene, $C_{10}H_{16}$, a terpene.

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

ACTIONS AND USES

Caraway acts like other **aromatic** drugs. It is extensively used as a flavouring and carminative agent.

Coriandrum.—Coriander Fruit. The dried ripe fruit of Coriandrum sativum. N.O. Umbelliferæ.

CHARACTERS.—Small brownish-yellow, globular fruits with sepals and styles; mericarps united with two oil glands internally; external primary ridges wavy, secondary straight. Odour aromatic; taste agreeable, spicy.

COMPOSITION.—The *Volatile Oil* (0·3%).

Oleum Coriandri.—The oil distilled from Coriander Fruit.

CHARACTERS.—Colourless or pale yellow; odour and taste of the fruit.

COMPOSITION.—*Coriandrol* (linalol), an acyclic alcohol, $C_{10}H_{17}OH$; *pinenes*; *geraniol* and *borneol* and an unknown *aromatic body.*

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

ACTIONS AND USES

The actions and uses of Coriander are those of other **aromatic** substances. Its flavour specially covers the tastes of Senna and Rhubarb.

Fœniculum.—Fennel Fruit. The dried ripe fruit of Fœniculum vulgare. N.O. Umbelliferæ.

CHARACTERS.—Brownish, large mericarps with pedicel, taperings, with five ridges and six large oil glands. Odour, aromatic; taste sweet, like camphor.

COMPOSITION.—A yellow *Volatile Oil* (1·4%), containing a phenol ether, *anethole,* $C_9H_9.OCH_3$, and a cyclic ketone, *fenchone,* $C_9H_{16}C = O$, also terpenes.

ACTIONS AND USES

Fennel has the same actions, and is used for the same purposes, as other **aromatic** substances.

Cardamomi Fructus.—Cardamom Fruit. The dried ripe fruit of Elettaria Cardamomum. N.O. Scitamineæ. The seeds only are used.

CHARACTERS.—Pale buff, ovoid, triangular pericarps. *Seeds:* reddish-brown, angular, and wrinkled. Odour aromatic; taste aromatic, warm.

COMPOSITION.—The active principle is a *Volatile Oil* (4%), containing *cineole*, *terpineol* and *limonene*.

Preparation

Tinctura Cardamomi Composita.—Cardamom seed, 1·4%; Caraway, 1·4%; Cinnamon, 2·8%; with Cochineal, Glycerin and Alcohol 60%. By percolation.

Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Cardamom Seeds and the Tincture are highly agreeable, slightly stimulant, **flavouring** and **carminative agents.**

Caryophyllum.—Clove. The dried flower-buds of Eugenia Caryophyllus. N.O. Myrtaceæ.

CHARACTERS.—A dark-brown, angular calyx tube showing four rigid sepals and four paler petals enclosing stamens and style; odour fragrant; taste pungent, aromatic.

COMPOSITION.—Clove contains 15% of the official *Volatile Oil*, tannic acid, and a colourless, odourless, crystalline body, *caryophyllin*, probably a phytosterol.

Preparations

1. **Infusum Caryophylli Concentratum.**—Concentrated Infusion. About 20% in Alcohol 25%.

Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

2. **Infusum Caryophylli.**—Concentrated Infusion 12·5% in Distilled Water.

Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

Oleum Caryophylli.—Oil of Cloves (by distillation).

CHARACTERS.—Colourless or pale yellow, darkening with age; odour and taste of Cloves. Contains at least 85% of eugenol.

COMPOSITION.—The oil contains a phenol-ether, *eugenol*, $C_9H_8.OH.OCH_3$; a terpene, *caryophyllene*, $C_{15}H_{24}$; *furfural*, $C_5H_4O_2$; *aceteugenol* and *methyl amyl ketone*, $C_5H_{11}COCH_3$.

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

ACTIONS AND USES

Oil of Cloves, applied externally (1 to 2 per cent. in Olive Oil) is a **rubefacient** for neuralgic and rheumatic pains. In dental practice, it is **obtundent** and **antiseptic**, allaying the pain of sensitive dentine or exposed pulp; it is used also to sterilize root canals and as an antiseptic in tooth pastes. Internally, Cloves and its preparations are valuable **carminatives** to alleviate colic and griping.

Myristica.—Nutmeg. The dried kernel of Myristica fragrans. N.O. Myristicaceæ.

CHARACTERS.—Oval, brown, furrowed kernels, marked with black; cross-section, marbled. Odour aromatic; taste aromatic, warm, somewhat bitter.

COMPOSITION.—The official *Volatile Oil* about 10%; *myristin*, and other fats 35%.

Oleum Myristicæ.—The oil distilled from Nutmeg.

CHARACTERS.—Colourless or pale yellow, with odour and taste of nutmeg.

COMPOSITION.—A terpene, *d-camphene*, $C_{10}H_{16}$; *myristicin*, $C_{11}H_{12}O_3$; and other aromatic substances.

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

ACTIONS AND USES

Nutmeg is an aromatic **carminative**, used chiefly in cookery, but it and the Volatile Oil are suitable to relieve colic and griping.

Cinnamomum.—Ceylon Cinnamon Bark. The dried inner bark of shoots of Cinnamomum zeylanicum. N.O. Laurineæ.

CHARACTERS.—Thin and brittle, yellowish-brown, closely rolled, compound quills. Odour fragrant; taste warm, sweet, aromatic.
COMPOSITION.—The official *Volatile Oil, tannic acid* and *mucilage.*

Oleum Cinnamomi.—The oil distilled from Cinnamon.

CHARACTERS.—Yellow when recent, becoming reddish; odour and taste of Cinnamon Bark.
COMPOSITION.—Contains *cinnamic aldehyde,* $C_6H_5.C_2H_2.CHO$, 60% and *eugenol,* 6%, with terpenes.
Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

Preparation

Aqua Cinnamomi Concentrata.—Oil of Cinnamon, 2% in Alcohol 90% and Distilled Water. *Diluted with* 39 *parts of Water for use as an Aromatic Water.*
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

ACTIONS AND USES

Cinnamon, besides possessing the same actions and being used for the same purposes as other **aromatic** substances, is slightly **astringent** in virtue of its tannic acid. The oil, given on sugar or sucked in tablets, is a popular remedy for laryngitis and influenzal colds.

Zingiber.—Ginger. Unbleached Jamaica Ginger. The scraped, dried rhizome of Zingiber officinale. N.O. Scitamineæ.

CHARACTERS.—Flattish, irregularly branched pieces, with a depressed apical scar; fracture short, but fibres project. Odour agreeable, aromatic; taste pungent.
COMPOSITION.—Ginger contains an *Aromatic Volatile Oil,* composed of *camphene, phellandrene, zingiberene, cineole* and *borneol*; a yellow pungent phenol, *gingerol*; *resin* and *starch.*
Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

Preparations

1. **Tinctura Zingiberis Fortis.**—Strong Tincture of Ginger. 50% in Alcohol 90%, by percolation.
Dose.—Metric, 0·3 to 0·6 Mil; Imperial, 5 to 10 min.
2. **Tinctura Zingiberis Mitis.**—Weak Tincture of Ginger. Strong Tincture, 20% in Alcohol 90%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
3. **Syrupus Zingiberis.**—Syrup of Ginger. Strong Tincture 5% in Syrup.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.

ACTIONS AND USES

Ginger acts and is used like **aromatic** Volatile Oils. It is one of the most generally employed of **carminatives**, and is rather moer pungent than most Volatile Oils.

Oleum Cajuputi.—Oil of Cajuput. The oil distilled from the leaves of Melaleuca Leucadendron. N.O. Myrtaceæ.

CHARACTERS.—Colourless or yellow; odour agreeable, camphoraceous; taste aromatic, bitter, camphoraceous.

COMPOSITION.—*Cineole* (eucalyptol), $C_{10}H_{18}O$, at least 50%; a crystalline alcohol, *terpineol*, $C_{10}H_{17}OH$; *l-pinene*, $C_{10}H_{16}$; and *valerianic* and *benzoic aldehydes*.

Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

Preparation

Spiritus Cajuputi.—10 in 100 of Alcohol 90%.

Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.

ACTIONS AND USES

Cajuput Oil is used externally as a **stimulant** and **counter-irritant** for inflamed and rheumatic joints. Internally, it and the Spirit act like Volatile Oils and are **carminative**.

Oleum Lavandulæ.—Oil of Lavender. The oil distilled from the flowers of Lavandula officinalis. N.O. Labiatæ.

CHARACTERS.—Pale yellow or yellowish-green, with the fragrant odour of the flowers, and a pungent bitter taste.

COMPOSITION.—An acyclic alcohol, *linalol*, $C_{10}H_{17}OH$; its ester, *linalyl acetate*, $C_{10}H_{17}.CH_3.COO$, of which there should be in English oil 7 to 12%, in foreign oil 35%; also terpenes, *pinene*, *limonene*; a sesquiterpene; and *geraniol*.

ACTIONS AND USES

Lavender possesses the actions of **aromatic** Volatile Oils in general. It is used chiefly as a **flavouring** agent for lotions or ointments and externally to repel insects. Internally it is seldom used even as a flavour.

Oleum Rosmarini.—Oil of Rosemary. The oil distilled from the flowering plant, Rosmarinus officinalis. N.O. Labiatæ.

CHARACTERS.—Colourless or pale yellow; odour of rosemary; taste warm, camphoraceous.

COMPOSITION.—Not less than 9% of total alcohols as *borneol*, $C_{10}H_{17}OH$; and 2% of esters as *bornyl acetate*, $C_{10}H_{17}CH_3.COO$.

ACTIONS AND USES

Rosemary resembles the other **aromatic** oils in its actions and uses. It is a common component of stimulating liniments.

Valeriana.—Valerian Rhizome. The dried rhizome and roots of Valeriana officinalis. N.O. Valerianeæ.

CHARACTERS.—A short, brown rhizome, with slender, brittle roots; internally, whitish. Odour strong, characteristic, disagreeable; taste unpleasant, camphoraceous, slightly bitter.

COMPOSITION.—A *Volatile Oil*, present in 1%, which contains *bornyl isovalerate*, *formate*, *butyrate*, and *acetate*, mixed with *l-pinene*, *l-camphene*, and *terpineol*. By ferment decomposition *isovaleric acid*, $C_5H_{10}O_2$, an oily liquid with a powerful valerianic odour and acrid burning taste, is formed.

Preparation

Tinctura Valerianæ Ammoniata.—Valerian Rhizome, 20%; Dilute Solution of Ammonia, 10% with Oil of Nutmeg and Oil of Lemon in Alcohol 60%; by maceration.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Valerian acts essentially like other substances containing Volatile Oils, but its pungent taste and disagreeable odour have a peculiarly powerful effect reflexly on the central nervous system. The oil and the acid are excreted in the urine, breath and sweat.

Valerian is used as a powerful **carminative** and reflex **nervous stimulant** and **antispasmodic**, in flatulence, fainting, spasms of hysterical origin and in malingering. The Ammoniated Tincture is a suitable preparation in such cases, as the Ammonia is also a reflex stimulant.

Tincture of Asafetida was formerly used for the same purposes.

Myrrha.—Myrrh. An oleo-gum-resin obtained from the stem of Commiphora Molmol. N.O. Burseraceæ.

CHARACTERS.—Rounded, reddish-yellow tears or masses; fractured surface translucent, and oily; odour aromatic; taste aromatic, bitter, acrid.

COMPOSITION.—Myrrh contains *gum*, 60%; volatile oil, 5%; and a resin, 35%.

Preparation

Tinctura Myrrhæ.—Myrrh, 20% in Alcohol 90%. Macerate.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Tincture of Myrrh is a mild aromatic **antiseptic** and **demulcent** upon the mucous membrane of the mouth, and throat. It is much employed in tooth-powders, as a wash (Tincture 1, Water 30) in spongy and ulcerated gums, and as a gargle in pharyngitis.

The Tincture is sometimes given as a **stomachic** and **carminative** in atonic dyspepsia, while, as a **reflex expectorant**, it is occasionally prescribed in chronic bronchitis.

Acidum Hydrocyanicum Dilutum (*not official*).—Dilute Prussic Acid. HCN. A 2% aqueous solution.

CHARACTERS.—A colourless liquid, odour characteristic.
Dose.—Metric, 0·12 to 0·3 Mil; Imperial, 2 to 5 min.

Hydrocyanic Acid is contained in Cherry-Laurel, Prunus Serotina, and Bitter Almonds.

ACTIONS AND USES.—Dilute Hydrocyanic was formerly used as a flavouring agent.

In the stomach, by paralysing the sensory endings, it acts as a **gastric sedative** and was prescribed to relieve gastric pain, and to arrest vomiting. It is absorbed rapidly and excreted partly through the lungs, and was used as a bronchial sedative in cough mixtures. Cyanides are excreted, principally in the urine, as sulphocyanides.

Toxic Actions.—Dilute Hydrocyanic Acid and Scheele's Prussic Acid (4%) are swift poisons. The fatal dose of HCN is about 0·05 G; this is present in 2·5 Mils (45 min.) of the Dilute Acid or in sixty Bitter Almonds; cyanides are fatal in dose of 0·3 G (5 gr.). The acid being volatile, severe poisoning may arise from inhaling the gas in dilutions of 1 : 10,000.

When taken by mouth there is a preliminary sensation of warmth, then numbness. Owing to the speed of absorption, poisonous symptoms occur almost immediately after large doses and are rarely delayed beyond a few minutes; death ensues in from five minutes to an hour.

The essential cause of poisoning by Hydrocyanic Acid is the **paralysis of the intracellular enzyme, cytochrome-oxidase,** with the result that the cells are unable to dissociate the oxygen from oxyhæmoglobin and consequently the tissues suffer immediately from anoxia. The venous blood in cyanide poisoning is arterial in colour and contains oxyhæmoglobin. During life Hydrocyanic Acid does not combine with hæmoglobin but, after death from it, the bright-crimson cyan-methæmoglobin may be seen in dependent parts.

The *symptoms of poisoning* are due entirely to the onset of anoxia, which causes brief stimulation, followed by paralysis, of the cerebrum and medulla. Violent headache, giddiness or faintness generally precede the medullary stimulation which causes accelerated and deepened respiration, marked slowing of the heart with, however, raised blood-pressure from vaso-constriction; vomiting may also occur. The pupils are dilated, the eyes protruded and the patient suffers from dyspnœa and a sense of constriction in the chest. Unconsciousness supervenes and asphyxial convulsions follow; from medullary depression the respiration now becomes retarded and shallow, blood-pressure falls but the heart remains slow and weak because the heart muscle is now directly poisoned. Death follows arrest of respiration.

Antidotes.—Treatment must be immediate. Inhalation of Amyl Nitrite and, if breathing ceases, artificial respiration; if not, slow intravenous injection of 10 Mils (150 min.) of 3% Sodium Nitrite solution, followed by 50 Mils (1½ fl. oz.) of 25% Sodium Thiosulphate to form sulphocyanides, but there is rarely time. Artificial respiration aids excretion and should be continued till the heart stops.

Prunus Serotina.—Wild Cherry Bark. Virginian Prune Bark. The bark of Prunus serotina. N.O. Rosaceæ.

CHARACTERS.—Curved pieces showing a thin, brown cork, or cortex, marked with lenticels; inner surface reddish-brown, striated. Odour slight; taste, recalling bitter almonds, astringent.

COMPOSITION.—A glycoside of *d-mandelonitrile*, $C_6H_5.CH.CN.OH$, and an enzyme *prunase*, which in presence of water yield benzaldehyde, hydrocyanic acid and dextrose ($C_{14}H_{17}NO_6 + H_2O = C_6H_5.CHO + HCN + C_6H_{12}O_6$); *volatile oil*, a bitter crystalline *glycoside*, and *tannic acid*.

Preparation

Syrupus Pruni Serotinæ.—Wild Cherry Bark, 15% in Sucrose, Glycerin and Water. Macerate and percolate.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.

ACTIONS AND USES

Virginian Prune Syrup acts as a **flavour** and **gastric sedative** by virtue of its content of Hydrocyanic Acid and Volatile Oil. It is mainly used as an aromatic adjuvant in mixtures in order to relieve cough by the sedative action of the Hydrocyanic Acid on the sensory endings in the bronchioles.

IV.—SWEETENING AGENTS

Sucrosum.—Refined Sugar. Sucrose. $C_{12}H_{22}O_{11}$. A crystallized sugar obtained from the juice of the sugar cane or sugar beet.

CHARACTERS.—Familiar. *Solubility.*—2 in 1 of water; solution dextro-rotatory.

Preparation

Syrupus.—Sucrose, 66·7% in Distilled Water; dissolved by heat.

ACTIONS AND USES

Sugar and Syrup are **nutritive**, but in pharmacy they are used chiefly as sweetening agents and diluents for other drugs or as demulcents. Sugar has been given orally in large doses, 60 to 120 G (2 to 4 oz.), and also intravenously (10 per cent. solutions are isotonic) in cardiac failure; hypertonic solutions (200 Mils of 50 per cent.) are injected intravenously to lower intracranial pressure in acute uræmia, and cerebral tumour.

Lactosum.—Milk Sugar. Saccharum Lactis. Lactose. $C_{12}H_{22}O_{11}$, H_2O. A crystallized sugar from whey of Milk.

CHARACTERS.—A white crystalline powder; taste, faintly sweet. *Solubility.*—1 in 7 of water; solution dextro-rotatory.

ACTIONS AND USES

Milk Sugar is a good diluent **vehicle** for powders. It is also used to sweeten diluted cow's milk for artificially-fed infants. In doses of 100 G (3 oz.) each day, it is **diuretic**, and slightly laxative. It is a useful nutrient in dyspepsia, being less sweet than Refined Sugar and less likely to ferment. Large doses of Lactose are of value in carbohydrate fermentation and are given with B. acidophilus to alter the intestinal bacterial flora in chronic diarrhœa.

Dextrosum.—Dextrose. $C_6H_{12}O_6$. Anhydrous Medicinal Glucose. Prepared by hydrolysis of starch.

CHARACTERS.—A white crystalline or granular powder; odourless; taste sweet. *Solubility.*—1 in 1 of water.

Preparations

1. **Injectio Dextrosi.**—Contains 5% in Water for Injection.
2. **Injectio Sodii Citratis cum Dextroso** (*see* p. 44).

Glucosum Liquidum.—Liquid Glucose. A syrupy mixture of dextrose, maltose, dextrin and water, obtained by hydrolysis of starch.

CHARACTERS.—Very viscid, almost colourless syrup; taste sweet. *Solubility.*—Freely in water; solution, dextro-rotatory.

Preparation

Syrupus Glucosi Liquidi.—Liquid Glucose, 33%, in Syrup. Syrup of Glucose is used as an excipient in most pills.

ACTIONS AND USES

Dextrose and Glucose are easily assimilated carbohydrates which are given by mouth during acute infective fevers, to infants with persistent vomiting from acidosis or ketosis, and as protectives to the liver in catarrhal jaundice and hepatitis. Injectio Dextrosi is isotonic and, given intravenously or by rectal injection (250–300 c.c.), is a rapid means of **increasing the blood-volume** and -pressure as well as a valuable **nutrient** for the treatment of acute circulatory failure, surgical shock and wasting diseases. In the acute fevers, pneumonia, recurrent vomiting, hæmatemesis, acute yellow atrophy, and after gastric operations, Dextrose injections intravenously, or rectally, serve as nutrients when food cannot be taken by mouth.

If symptoms of **ketosis** or coma develop during diabetes mellitus, Dextrose injections (20 to 50 G in 5 or 10 per cent. solutions) are essential along with Insulin therapy and, if **hypoglycæmia** arises during Insulin treatment, Dextrose, 4 to 20 G (60 to 300 gr.), orally, rectally, or, if urgent, intravenously, must be given (*see* p. 207). Dextrose administration may also be necessary to ensure an adequate reserve of carbohydrate prior to prolonged operations and to avert or treat delayed Chloroform poisoning and poisoning by Organic Arsenicals, Cinchophen or Carbon Tetrachloride.

Intravenous injections of 25 or 50 per cent. Dextrose solutions lower intracranial pressure by osmosis and are used in hydrocephalus, meningitis, cerebral tumour and acute uræmia. Anuria may be overcome by giving an intravenous drip of 500 Mils of 10 per cent. Dextrose with 4·285 per cent. Sodium Sulphate in Normal Saline Solution.

Dextrosum Hydratum.—Dextrose Monohydrate. Medicinal Glucose. $C_6H_{12}O_6,H_2O$.

CHARACTERS.—Colourless crystals or a white powder; taste sweet. *Solubility.*—1 in 1 of water.

USES

This is the most suitable form of Dextrose for oral use by diabetics, or for adding to infants' foods.

Lævulosum.—Lævulose. Fructose. $C_6H_{12}O_6$. The lævorotatory isomer of dextrose, made from invert sugar or honey.

CHARACTERS.—White or creamy, hygroscopic, crystalline powder; taste very sweet. *Solubility.*—Readily in water.

ACTIONS AND USES

Lævulose is much sweeter than Cane Sugar and is readily absorbed. As it is thought to be convertible more easily into glycogen than dextrose or other carbohydrates, it has been used as a **substitute for sugars** in diabetic cookery. Large doses, 200 G (6 oz.), have been given as nutrients in wasting diseases, especially in children.

The **lævulose tolerance test** is employed to estimate hepatic efficiency. A dose of 50 G (750 gr.) is given in water after a fast of 12 hours and blood-sugar estimations made at half-hourly intervals for two hours. A rise of 0·03 per cent. above the fasting level indicates hepatic disorder.

Saccharinum.—Saccharin. *o*-Benzoic-sulphimide.

Saccharinum Sodium.—Soluble Saccharin. Sodium Salt of *o*-Benzoic-sulphimide. $CO.C_6H_4.SO_2N.Na, 2H_2O$.

CHARACTERS.—A white crystalline powder; taste intensely sweet in dilute solutions. *Solubility.*—1 in 1·5 of water.

ACTIONS AND USES

Soluble Saccharin is used as a **sweetening agent**, and as a substitute for sugar in diabetes mellitus, corpulence and hepatic disorders. It is not a food, nor has it any deleterious effects.

V.—Bitter Stomachics

The Bitter Stomachics increase the functional activity of the digestive organs. There are (*a*) *Simple Bitters*; and (*b*) *Aromatic Bitters*, which combine an aromatic flavour with the bitter taste. Other drugs having a bitter taste, e.g. Strychnine and Quinine, produce the actions of Bitters.

A.—SIMPLE BITTERS

Calumba.—Calumba Root. The dried, transversely-cut root of Jateorhiza palmata. N.O. Menispermaceæ.

CHARACTERS.—Flattish, circular or oval slices, depressed centrally; cork brownish, cortex thick, yellowish, separated by a dark line from greyish wood. Odour feeble; taste bitter.

COMPOSITION.—Three yellow crystalline alkaloids, *jateorhizine*, $C_{20}H_{20}NO_5.OH$, *columbamine*, $C_{21}H_{22}NO_5.OH$, and *palmatine*, $C_{21}H_{22}NO_6.OH$; two colourless bitter, crystalline principles, *columbin* and *chasmantherin*; 35% of *starch*; but no tannic acid.

Preparations

1. **Infusum Calumbæ Recens.**—Fresh Infusion. 5 in 100 of *cold* Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.
2. **Infusum Calumbæ Concentratum.**—Concentrated Infusion. Calumba 40% with Alcohol 90% in cold Distilled Water.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
3. **Infusum Calumbæ.**—Concentrated Infusion 12·5% in Distilled Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.
4. **Tinctura Calumbæ.**—10 in 100 of Alcohol 60%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES OF BITTER STOMACHICS

Externally.—The Bitters are occasionally used, with soap, as insecticides.

Internally.—In the *mouth*, Bitters stimulate the taste buds; this induces reflexly a free **flow of saliva** and excites an increased **flow of secretion from the gastric glands**: this effect can be produced simply by washing out the mouth with a bitter substance. The most powerful excitant of gastric secretion is the taste of food, and it must be noted that, when the gustatory reflex is normal, Bitters will not increase it; but when appetite or taste for food fails, Bitters are effective excitants of the gustatory endings. In such circumstances Bitters, if given before meals, arouse a sense of hunger, excite appetite, and increase reflexly the gastric secretion; a further increase follows upon the taking of food, the pleasant flavours of which, as a contrast to the bitter taste, again stimulate the taste buds. The combination of an aromatic flavour and alcohol with a bitter taste, e.g. sherry, will obviously tend to augment these reflex actions.

In the *stomach*, Bitters do not directly increase the flow of gastric secretion and, in fact, retard peptic digestion slightly. Bitters should be given for brief periods only; their object is to arouse the normal psychical reflex to food and, when this is restored, they should be stopped. Prolonged use, by causing fatigue of the reflex, may diminish gastric secretion.

Aromatic Bitters possess similar actions to Simple Bitters but, as they have more pleasant tastes, the contrast between them and relishing food is less striking; they have, however, a carminative value.

In the *intestine*, Bitters have no special action. They increase the pancreatic secretion indirectly by augmenting the gastric acid.

After absorption, Bitters have no useful actions; the leucocytosis observed after their use is due purely to improvement in the digestive functions.

The uses of Calumba and other Bitters are based on these actions. They are of great value as **stomachics** and act indirectly, by improving digestion, as "**general tonics.**" Bitters are much employed to arouse the appetite in atonic dyspepsia, anæmia, convalescence from acute diseases, and in debilitated patients. They should not be given in acute gastritis, but may follow a sedative course of Bismuth in such cases. Bitters should be administered in solution—as an infusion or diluted tincture—about fifteen minutes before meals, and attempts to mask their taste avoided; in pilular form they are valueless. If Bitters are prescribed with salts of Iron, Quassia or Calumba, which contain no tannic acid, must be selected.

Quassia.—Quassia Wood. Jamaica Quassia. The stemwood of Picræna excelsa. N.O. Simarubeæ.

CHARACTERS.—Chips or raspings; yellowish-white, dense, tough. Inodorous; taste intensely bitter.

COMPOSITION.—*Quassin*, a mixture of two white, crystalline, neutral bitter principles, *a-picrasmin*, $C_{35}H_{46}O_{10}$, and *β-picrasmin*, $C_{36}H_{48}O_{10}$.

Preparations

1. **Infusum Quassiæ Recens.**—Fresh Infusion. 1 in 100 of *cold* Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.
2. **Infusum Quassiæ Concentratum.**—Concentrated Infusion. Quassia 8% with Alcohol 90% in cold Distilled Water.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

3. **Infusum Quassiæ.**—Concentrated Infusion 12·5% in Distilled Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial 1/2 to 1 fl. oz.
4. **Tinctura Quassiæ.**—10 in 100 of Alcohol 45%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Quassia is a **Simple Bitter**, and possesses the various properties just described. It is very extensively used. The special points to be noted respecting it are: (1) that its preparations contain no tannic acid, and may be prescribed with salts of Iron; (2) that it is entirely devoid of aroma, and intensely bitter, i.e. less agreeable than Gentian; and (3) that a 5 per cent. infusion forms an excellent anthelmintic enema for threadworm.

B.—AROMATIC BITTERS

Gentiana.—Gentian Root. The dried rhizome and root of Gentiana lutea. N.O. Gentianeæ.

CHARACTERS.—Nearly cylindrical, yellowish-brown pieces, longitudinally wrinkled; apex shows a bud or leaf-scars. Odour characteristic: taste at first sweet, bitter.

COMPOSITION.—Gentian contains two bitter *glycosides*, *gentiin* and *gentiamarin*; also *sugar*, and colouring matter, but *no starch.*

Preparations

1. **Infusum Gentianæ Compositum Concentratum.**—Concentrated Infusion. Gentian 10% with Dried Bitter-Orange Peel and Lemon Peel in Alcohol 25%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
2. **Infusum Gentianæ Compositum.**—Concentrated Infusion 12·5% in Distilled Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.
3. **Tinctura Gentianæ Composita.**—Gentian, 10%, with Dried Bitter-Orange Peel and Cardamom in Alcohol 45%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Gentian possesses the actions and uses of **Bitters**. It is perhaps the most popular of all Bitters, because: (1) it is agreeable, being very slightly **aromatic**; and (2) its bitter taste is not intense.

Aurantii Cortex Siccatus.—Dried Bitter-Orange Peel. The dried outer pericarp of Citrus Aurantium. N.O. Rutaceæ.

CHARACTERS.—Thin, deep orange-red strips, rough and glandular, nearly free from the white spongy part of the pericarp; odour aromatic, pleasant; taste bitter.

COMPOSITION.—2·5% of Volatile Oil, *oleum corticis aurantii*, an amorphous bitter glycoside, *aurantiamarin*, and a tasteless crystalline glycoside, *hesperidin.*

Preparations

1. **Infusum Aurantii Concentratum.**—Concentrated Infusion. Dried Bitter-Orange Peel 40% in Alcohol 25%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
2. **Infusum Aurantii.**—Concentrated Infusion 12·5% in Distilled Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

Aurantii Cortex Recens.—Fresh Bitter-Orange Peel. The fresh outer pericarp of Citrus Aurantium. N.O. Rutaceæ.

CHARACTERS.—Deep orange-red or red; rough and glandular; with little of the white spongy portion of pericarp; odour aromatic, pleasant; taste aromatic, bitter.

Preparations

1. **Tinctura Aurantii.**—25% in Alcohol 90%.
Dose,—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
2. **Syrupus Aurantii.**—Tincture, 12·5% in Syrup.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.

ACTIONS AND USES

Orange is an **aromatic and a Bitter**, and combines the actions of these two classes of remedies, as described under *Volatile Oils* (p. 144) and *Bitters* (p. 158) respectively. It is extensively used as a highly agreeable flavouring agent in cookery, pharmacy and the manufacture of liqueurs. It is a very weak Bitter. Orange juice contains Vitamin C.

Limonis Cortex Recens.—Fresh Lemon Peel. The fresh outer pericarp of Citrus Limon. N.O. Rutaceæ.

CHARACTERS.—Pale yellow and rough from oil-glands in epidermis; having little of the white spongy portion of rind. Odour strong, characteristic, fragrant; taste warm, aromatic and bitter.
COMPOSITION.—Lemon Peel contains the official *volatile oil, oleum limonis*, chiefly *limonene*, $C_{10}H_{16}$, and *hesperidin.*

Preparations

1. **Syrupus Limonis.**—Lemon Peel, 6%, with Citric Acid, 2·4%, in Alcohol 60% and Syrup.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.
2. **Tinctura Limonis.**—Lemon Peel, 25% in Alcohol 90%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

Limonis Cortex Siccatus.—Dried Lemon Peel is contained in compound concentrated Infusion of Gentian.

Oleum Limonis.—Oil of Lemon, expressed from Lemon Peel.

CHARACTERS.—Pale yellow; volatile; odour of lemons; taste warm, slightly bitter, aromatic.

COMPOSITION.—Terpenes *d-limonene*, *terpinene* and *phellandrene*; and not less than 4% of aromatic aldehydes *citral*, $C_9H_{15}CHO$, and *citronellal*, $C_9H_{17}CHO$.

ACTIONS AND USES

The actions and uses of Lemon Peel are the same as those of Orange, the only difference being in the flavour.

Lemon Juice, which contains 7 to 9 per cent. of Citric Acid, is a pleasant way of giving this acid as a refrigerant to relieve thirst in fever, and is also used, with Bicarbonates, to prepare effervescent drinks. The acid is absorbed as Citrates which are excreted by the kidneys as Bicarbonates and lower the urinary acidity. Lemon Juice contains the antiscorbutic Ascorbic Acid (Vitamin C).

VI.—DIGESTIVES

Digestive ferments.—Both proteolytic and amylolytic enzymes of animal or vegetable origin are used to replace deficiencies in the natural digestive ferments.

Pepsinum.—Pepsin. A powder containing a proteolytic enzyme obtained from the fresh gastric mucous membrane of the pig, sheep, or calf.

CHARACTERS.—A light yellowish-brown powder, taste slightly acid or saline. *Solubility.*—1 in 50 of water, more so if acid. Dissolves, with water acidulated with Hydrochloric Acid, 2,500 times its weight of coagulated egg-albumen within four hours. *Incompatible* with alkalis and tannic acid.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

The enzyme Pepsin converts proteins through acid metaprotein, primary and secondary proteoses into peptone. Pepsin digests proteins in acid media only, the optimum percentage of HCl being 0·4 per cent.; alkalis destroy the enzyme rapidly. Powdered Pepsin is best given during meals on buttered toast and followed by a draught containing a suitable dose of Dilute Hydrochloric Acid, or the Pepsin may be dissolved in the acid draught, or given in a mild wine.

It must be noted that the gastric juice is seldom deficient in enzyme but frequently contains too little acid; and Pepsin is unnecessarily prescribed as an aid to digestion in dyspepsias and debility. It has a restricted use in the atrophic dyspepsias of the aged and in gastric carcinoma.

Pancreatinum.—Pancreatin. An alcoholic (25%) extract of the pancreas, containing the enzymes *trypsin*, *amylase* and *lipase*.

CHARACTERS.—A colourless, or buff, amorphous powder; odour meaty. *Solubility.*—Readily in water, solution turbid. Assayed to prove a standard activity of the three enzymes.
Dose.—Metric, 0·2 to 0·6 G; Imperial, 3 to 10 gr.

ACTIONS AND USES

Trypsin decomposes proteins into polypeptides and amino-acids; amylase converts starch into maltose; and lipase splits fats into fatty acids and glycerol. Pancreatin acts only in an alkaline medium; it is destroyed by acids and, if given by mouth, must be taken in keratin-coated capsules or with Bicarbonates before meals when gastric acidity is low. Pancreatin has been used in rare cases of inefficient pancreatic secretion or of obstruction in the duct.

Pancreatin is used, with four parts of Sodium Bicarbonate, chiefly to **peptonize foods**, e.g. milk, gruel, soup, and beef-tea, which, if the foods are only partially (15 minutes) pancreatized, will lack the bitter and nauseous taste of fully peptonized foods, and can be taken by mouth. Amino-acids are absorbed only to a slight extent by the rectum, hence pancreatized foods have little nutrient value when given as enemata.

Papain, Papayotin, is a white amorphous powder obtained from the juice of Carica Papaya. N.O. Cucurbitaceæ. *Dose.*—0·12 to 0·6 G (2 to 10 gr.). It digests proteins in acid, alkaline or neutral media. It is used as a *digestive* in chronic dyspepsia and gastric fermentation.

Seriparium. Rennin or Rennet, is a buff powder, prepared from the calf's fourth stomach by extraction with salt solution. Rennin curdles milk by converting, in the presence of calcium salts, caseinogen into casein. It is used in cookery to make curds and milk whey, either in the form of a 30% solution (Essence of Rennet), of which 1 to 2 fl. dr. coagulates 20 fl. oz. of milk at 38° C., or as tablets.

VII.—EMETICS

Emetics cause, through the medullary vomiting centre, powerful contractions of the abdominal muscles, resulting in compression of the stomach against the diaphragm which is fixed in the inspiratory position; the cardiac sphincter of the stomach is relaxed, and ejection of the gastric contents—vomiting—results. They act in two ways: (1) *Central Emetics*, which directly stimulate the vomiting centre, e.g. Apomorphine; (2) *Reflex Emetics*, which, by irritation of a sensory receptor, usually the sensory endings of the vagus in the stomach, reflexly stimulate the vomiting centre, e.g. Ipecacuanha, Tartar Emetic, Ammonium

Bicarbonate, Copper and Zinc Sulphates, Alum, Mustard, and Sodium Chloride. The reflex emetics have other important uses but their emetic action should be compared with that of Apomorphine.

Apomorphinæ Hydrochloridum.—Apomorphine Hydrochloride. $C_{17}H_{17}NO_2$, HCl, $\frac{1}{2}H_2O$. The alkaloid is obtained from Morphine by the abstraction of a molecule of water.

CHARACTERS.—Small, greyish-white, shining needles, turning green on exposure. *Solubility.*—1 in 50 in water; solutions decompose if overheated. *Tests.*—$NaHCO_3$ forms a white precipitate which becomes green on standing, and then forms a purple solution with ether, bluish with chloroform, and green with alcohol 90%. With dilute solution of ferric chloride it gives a deep-red coloration.

Dose.—*Emetic, hypodermically:*

Metric, 2 to 8 mg.; Imperial 1/32 to 1/8 gr.

Preparation

Injectio Apomorphinæ Hydrochloridi.—A sterile solution, containing Sodium Metabisulphite, in Distilled Water. Contains 3 mg. (1/20 gr.) in 1 Mil (15 min.). Decomposes on keeping; if green, reject.

ACTIONS AND USES

Apomorphine is the most certain of all emetics. It is a central emetic acting purely by stimulation of the vomiting centre in the medulla, as is proved by the facts that (*a*) it acts more quickly when injected than if taken orally, (*b*) it does not act if the vessels to the medulla have been tied but (*c*) acts promptly if applied directly to the medulla. When it is injected subcutaneously in emetic dosage, moderate nausea and repeated vomiting occur usually in about five minutes. The symptoms of nausea accompany its action—salivation, perspiration associated with a feeling of cold, and increased secretion from the mucous glands of the nose, throat and bronchi. The pulse and respiration are increased in frequency. Complete evacuation of the stomach contents occurs; the nausea and vomiting subside rapidly when the stomach is empty.

Apomorphine is particularly useful as an emetic in poisoning, since it does not irritate the stomach nor induce untoward after-effects, but acts promptly and with certainty; it is of special value where the patient is comatose and unable to swallow; in narcotic poisoning, however, depression of the vomiting centre may delay or prevent its action.

Even in sub-emetic dosage Apomorphine often induces sleep, and when given hypodermically in emetic dosage, it is an effective **hypnotic.** This is particularly useful in **acute alcoholism,** because, following the emesis which removes the alcohol, deep and refreshing sleep supervenes within a few minutes and lasts about 12 hours.

In small doses, Apomorphine induces only slight nausea, but its stimulation of the vomiting centre induces through the secretory vagus fibres an increase in the mucous secretion of the bronchial glands. Apomorphine is thus an **expectorant**; small doses 1 to 2 mg. (1/60 to 1/30 gr.), by mouth, or in urgent cases hypodermically, are used in bronchitis to assist cough by liquefying tough secretion. The action although rapid is not lasting, therefore Apomorphine is not employed as a routine expectorant.

VIII.—PURGATIVES

Purgatives are drugs which cause evacuation of the intestinal contents. *Vegetable* purgatives may be grouped into those acting (1) physically; (2) in the small intestine; (3) in the large intestine; and (4) in both the small and large intestines. The terms *laxative*, or *aperient*, *simple purgative*, *hydragogue purgative*, and *drastic purgative* or *cathartic* are rather loosely used to represent increasing degrees of purgative potency, but this is also modified by dosage.

1. PURGATIVES ACTING PHYSICALLY

These increase the action of the bowels either (1) by augmenting their contents and thus reflexly increasing peristalsis, or (2) by lubricating the bowel, e.g. Liquid Paraffin.

In moderated degrees of constipation, the patient should be advised to adopt a regular daily time for evacuation, and advantage may be taken of the gastro-colic reflex in recommending the time to be immediately after breakfast. The adoption of a regular habit may be all that is necessary; but the diet should be reviewed because, if it is one which leaves little residue, there may be insufficient stimulus for peristalsis. In such cases the diet must be modified by the addition to it of food which will leave a substantial amount of insoluble cellulose in the bowel, namely, wholemeal bread, porridge, vegetables, particularly the cabbage family, and fruits, especially prunes and figs; tamarinds and cassia pulp were formerly official laxative fruits. Fruits, besides leaving a residue of cellulose, also contain salts—tartrates and malates—and sugars, which, by raising the osmotic tension in the bowel, can have a saline purgative action. Only one laxative, acting physically, is official, namely Agar.

Agar.—Agar-Agar. A dried, gelatinous substance obtained from various algæ, e.g. Gelidium Amansii. N.O. Rhodophyceæ.

CHARACTERS.—Yellowish, translucent strips, or a greyish powder. Insoluble, but swells to a jelly in cold water.

COMPOSITION.—A carbohydrate, *gelose*, which hydrolyses to *galactose*.

Dose.—Metric, 4 to 16 G; Imperial, 60 to 240 gr.

ACTIONS AND USES

Agar is not digested, but absorbs moisture and swells in the alimentary tract to form soft gelatinous masses. These make the intestinal contents more bulky and **peristalsis** is **reflexly augmented**; a soft formed stool is evacuated in about 8 to 12 hours. Agar should be given as shreds or the powder dispersed in food, otherwise clumps of jelly may form and cause colic. Agar is also employed for bacteriological media.

Agar is a useful **laxative** in mild forms of intestinal atony and chronic constipation; it is frequently used to treat constipation in children.

Psyllium Seeds (B.P.C.) from Plantago psyllium contain mucilage and swell in water to form jelly-like pilules. From one to four teaspoonfuls (4 to 16 G), after soaking in water overnight, are taken as a laxative.

Paraffinum Liquidum, which acts as a laxative by lubricating the bowel and its contents, is discussed on p. 388.

2. PURGATIVES ACTING IN THE SMALL INTESTINE

These increase peristalsis reflexly by irritation of the small intestine, and give rise to a single soft, but not watery, stool in ordinary dose.

Oleum Ricini.—Castor Oil. A fixed oil expressed from the seeds of Ricinus communis. N.O. Euphorbiaceæ.

CHARACTERS.—A colourless or yellowish viscid liquid. Odour slight; taste bland at first, then acrid and unpleasant.

COMPOSITION.—Chiefly *ricinolein*, a mixture of glycerides of *ricinoleic acid*, $C_3H_5(C_{18}H_{33}O_3)_3$, and *isoricinoleic acids*; glycerides of *stearic* and *dihydroxystearic acid*.

Dose.—Metric, 4 to 16 Mils; Imperial, 60 to 240 min.

ACTIONS AND USES

Externally.—Castor Oil is a bland fixed oil and may be used as a local **sedative and protective**. It is used as an emollient in hair lotions; as a solvent for alkaloids intended for application to the eye; and to allay the irritation and aid the removal of foreign bodies on the conjunctiva.

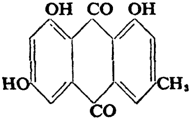
Internally.—Castor Oil is inactive in the stomach, but in the alkaline intestine is **hydrolysed by lipase into alkali ricinoleates and glycerol**. These ricinoleates act as irritants to the nerve endings in the small intestine; reflexly, this causes increased peristalsis, so that the fluid contents are hurried into the colon. The colon is not irritated, because the fatty acid and glycerol have been absorbed from the small intestine, but, owing to the arrival of the bulky fluid contents, anti-peristalsis is diminished, and evacuation of the colon soon occurs. The irritant action on the small intestine is confined to the upper part; it is of a mild character and causes no inflammation or griping. **Purgation** results in from four to eight hours according to the dose. A soft but not watery stool is voided without straining or irritation of the anus; intestinal quiescence follows for about a day.

Castor Oil is a useful purgative where simple evacuation of the bowels is desired. Its taste may be masked by giving it in milk or cold coffee, or it may be prescribed in emulsion, flavoured with Peppermint or Cinnamon. For children, Aromatic Castor Oil (B.P.C.) is available. For a rapid action, it should be given in the morning on an empty stomach; otherwise evening is the suitable time. It is specially employed in the treatment of diarrhœa due to the presence of indigestible or unwholesome food in the bowel, and may then be followed by Pulvis Cretæ Aromaticus cum Opio. Castor Oil is also given in the constipation of fevers; after abdominal operations; in the intestinal colic of children; and for nursing mothers. It is valuable in pregnancy, and in hæmorrhoids, because it causes no pelvic or rectal congestion; repeated small doses are successfully given in the intestinal indigestion of artificially-fed infants.

Ricin, a toxalbumose, is present in Castor Oil seeds but not in the oil. Injections of Ricin cause agglutination of the red cells and lead to gastro-intestinal inflammation and hæmorrhages. Repeated small injections establish immunity, owing to the formation of an antitoxin, antiricin, in the blood.

3. PURGATIVES ACTING ON THE LARGE INTESTINE

Anthracene purgatives owe their action to the presence of inactive glycosides which are absorbed and slowly hydrolysed by the body into compounds of *anthracene*, $C_{14}H_{10}$. The most important of these are *emodin*, or trihydroxy-methyl-anthraquinone, $C_{14}H_4(CH_3)(OH)_3O_2$, and *chrysophanic acid*, or dihydroxy-methyl-anthraquinone, $C_{14}H_5(CH_3)(OH)_2O_2$.



Emodin

Anthracene purgatives act upon the large intestine. Their glycosides were formerly thought to be hydrolysed slowly in the bowel and to be effectively irritant only in the colon; but, because they produce colonic peristalsis after a time if a dose is confined within the small intestine and also after a latent period if given by injection, the glucosides must be absorbed from the small intestine and hydrolysed by the tissues to form the active emodin which stimulates the colonic muscle directly on reaching it through the circulation.

Cascara Sagrada.—Cascara Sagrada. The dried bark of Rhamnus Purshianus. N.O. Rhamneæ.

CHARACTERS.—Quilled or nearly flat pieces. Cork smooth, purplish-brown, with elongated lenticels, and showing patches of silver-grey lichen. Inner surface, reddish-brown, striated. Odour characteristic; taste persistent, bitter, nauseous.

COMPOSITION.—Cascara contains *emodin* and *frangula-emodin* about 2%; *glucose*; fats and a bitter principle.

Preparations

1. **Elixir Cascaræ Sagradæ.**—Cascara, Liquorice, and Light Magnesium Oxide macerated and percolated with boiling water, evaporated and flavoured with Saccharin, Coriander and Anise Oils and Glycerin.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
2. **Extractum Cascaræ Sagradæ Siccum.**—Aqueous; dried.
Dose.—Metric, 0·12 to 0·5 G; Imperial, 2 to 8 gr.
3. **Extractum Cascaræ Sagradæ Liquidum.**—Alcoholic and aqueous; by percolation. 1 in 1.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Cascara Sagrada is the mildest anthraquinone purgative. Being bitter it acts as a **stomachic** in small doses. Cascara stimulates peristalsis in the **large intestine** and causes evacuation of a soft but formed stool. Excessive doses induce colic, griping and diarrhœa. Cascara acts as a **purgative** in about eight to twelve hours, usually giving rise to one motion, which does not empty the small intestine. As the dosage does not require to be increased with usage, Cascara is employed largely in the treatment of chronic constipation, particularly in aged persons. It is best given as tablets or pills containing the Dry Extract or as the pleasant Elixir in the evening and, by adjusting the dosage to the requisite minimum, it is often possible to assist restoration of the normal function by inculcating regular habits and modifying the diet. Since its stimulant action on the colon is moderate, Cascara may be used during pregnancy or by patients with hæmorrhoids.

Aloe.—Aloes. Cape, Curaçao, or Barbados Aloes. The dried juice from cut leaves of species of Aloe. N.O. Liliaceæ.

CHARACTERS.—Light to dark brown, glassy or opaque, hard masses. Odour characteristic; taste nauseous, bitter. *Solubility.*—Almost entirely in alcohol 60%.

COMPOSITION.—Aloes contains the glycoside, *aloin*; *aloe resin*; *aloe-emodin*; and a *volatile oil.*

Dose.—Metric, 0·12 to 0·3 G; Imperial, 2 to 5 gr.

Preparation

Pilula Aloes.—Aloes 58%; with Hard Soap, Oil of Caraway, and Syrup of Liquid Glucose.

Dose.—Metric, 0·25 to 0·5 G; Imperial, 4 to 8 gr.

Aloinum.—Aloin. $C_{21}H_{20}O_9$. A mixture of crystalline glycosides obtained from Aloes.

CHARACTERS.—A pale-yellow, micro-crystalline powder; inodorous; taste intensely bitter. *Solubility.*—1 in 130 of water.

COMPOSITION.—*Barbaloin*, $C_{21}H_{20}O_9$, and *isobarbaloin* in equal proportions. Barbaloin is a methyl-anthraquinone glycoside, which hydrolyses into *aloe-emodin* or trihydroxy-methyl-anthraquinone and *d*-arabinose.

Dose.—Metric, 15 to 60 mg.; Imperial, 1/4 to 1 gr.

ACTIONS AND USES

Aloes, in solution, is occasionally used as a **bitter stomachic.** Its chief action is **purgative**; the active principle, Aloin, consists of anthraquinone glycosides which, hydrolysed after absorption, exert a stimulant action on the colon, increasing its peristalsis. The Aloin glycosides are less easily hydrolysed than others and this may explain the slower action of this drug.

Therapeutic doses of Aloes cause purgation in from ten to twelve hours, the stool being soft and formed, or slightly loose; it is preceded and accompanied by some griping pain. The stimulant action of Aloes on the large bowel is apt to produce congestion of the mucous membrane and of the pelvic organs; therefore it is unsuitable as a purgative in hæmorrhoids and during menstruation or pregnancy.

Aloes is a valuable purgative because its effects do not decrease with continued use; hence it is given as an habitual aperient in constipation due to colonic atony, generally as pills or tablets, coated to mask its bitter taste, and along with carminatives to mitigate griping.

Its oral administration is believed to increase the uterine contractions owing to the absorption of Aloin; but it is more likely that large doses induce congestion of the pelvic organs; this would explain its unreliable emmenagogue and abortifacient effects.

Rheum.—Rhubarb. The dry rhizome, without bark, of Rheum palmatum, and other species, from China and Tibet. N.O. Polygonaceæ.

CHARACTERS.—Cylindrical or conical pieces, often perforated and covered with a brownish-yellow powder, marked with reddish-brown lines and small, starlike marks. Odour characteristic, somewhat aromatic; taste bitter, feebly astringent.

COMPOSITION.—Rhubarb Root contains purgative anthraquinone derivatives: *chrysophanic acid*, *emodin*, *rhein*, and *rheotannic acid*, which is an astringent. Starch and calcium oxalate are also present.

Dose.—Metric, 0·2 to 1 G; Imperial, 3 to 15 gr.

Preparations

1. **Pilula Rhei Composita.**—Rhubarb, 25%; Aloes, 20%; with Myrrh, Hard Soap, Oil of Peppermint, and Syrup of Liquid Glucose.
Dose.—Metric, 0·25 to 0·5 G; Imperial, 4 to 8 gr.
2. **Pulvis Rhei Compositus.**—"Gregory's Powder." Rhubarb, 25%; with Heavy and Light Magnesium Carbonates, 66% and Ginger.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.
3. **Tinctura Rhei Composita.**—Rhubarb, 10%; with Cardamom Seed, Coriander, Glycerin, and Alcohol 60%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Rhubarb differs from other anthraquinone purgatives in containing Tannic Acid. In small doses, it acts as a **bitter stomachic** and **gastric astringent**, and is often given with alkaline powders (Pulvis Rhei Co.) for dyspepsia, particularly in children; the later laxative effect is advantageous by removing indigestible food from the bowel.

When given as a **purgative**, Rhubarb stimulates the peristalsis of the large intestine. Evacuation of a soft motion accompanied by some griping occurs in from six to eight hours. After purgation, the **astringent** rheotannic acid has a sedative effect on the mucous membrane and diminishes the secretion, so that temporary constipation may follow. Rhubarb is therefore of value only when it is desired to empty the bowel of noxious material and is not suitable for treating chronic constipation.

Rhubarb is commonly used for children and adults to remove irritant or indigestible matter from the intestine and for the treatment of the summer diarrhœas of infancy; the Compound Powder is usually prescribed. The Compound Pill is employed as a brisk purge in colonic stasis.

The chrysophanic acid contained in Rhubarb stains the fæces yellow; some is also absorbed and is excreted by the kidneys, giving the urine a brownish or, if alkaline, a red colour.

Sennæ Folium.—Senna Leaf. The dried leaflets of Cassia acutifolia, Alexandrian Senna, or Cassia angustifolia, Tinnevelly Senna. N.O. Leguminosæ.

CHARACTERS.—Pale greyish-green, thin, lanceolate leaflets, about 2 to 4 cm. long; apex acute, *base unequal.* Odour peculiar, faint; taste mucilaginous, unpleasant.
COMPOSITION.—Senna contains *aloe-emodin*, $C_{14}H_4(CH_3)(OH_3)O_2$, *rhein*, *chrysophanic acid*, *kæmpferol* and *isorhamnetin* with their glycosides, and mucilage.
Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

Preparation

Pulvis Glycyrrhizæ Compositus.—Senna and Liquorice, 16% with Fennel, Sublimed Sulphur and Sucrose.
Dose.—Metric, 4 to 8 G; Imperial, 60 to 120 gr.

Sennæ Fructus.—Senna Pod. The dried ripe fruits of Cassia acutifolia or of Cassia angustifolia.

CHARACTERS.—Pale-green, oblong or reniform pods, centre brown; seeds flat, ovate. Odour and taste slight.
COMPOSITION.—As of the leaves.
Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

Preparations

1. **Extractum Sennæ Liquidum.**—Senna Fruit 1 in 1, with Oil of Coriander, Alcohol 90% and Chloroform Water.
Dose.—Metric, 0·6 to 2 Mils; Imperial, 10 to 30 min.
2. **Syrupus Sennæ.**—Liquid Extract 25% in Syrup.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.
3. **Infusum Sennæ Concentratum.**—Senna Fruit 80% with Strong Tincture of Ginger in Alcohol 20%.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.
4. **Infusum Sennæ.**—Concentrated Infusion 12·5% in Distilled Water; use within 12 hours.
Dose.—Metric, 15 to 60 Mils; Imperial, 1/2 to 1 fl. oz.
5. **Mistura Sennæ Composita.**—"Black Draught." Magnesium Sulphate, 25; Liquid Extract of Liquorice, 5; Compound Tincture of Cardamom, 10; Aromatic Spirit of Ammonia, 5; Infusion of Senna to 100.
Dose.—Metric, 30 to 60 Mils; Imperial, 1 to 2 fl. oz.

ACTIONS AND USES

Senna is the most active anthraquinone **purgative.** The preparations from Senna Pods are relatively more potent and less griping. Senna stimulates the colonic muscle and produces brisk peristaltic movements which hurry onward the fluid contents received from the ileum. Purgation accompanied by griping pains results in from four to eight hours, the stool being fluid, copious and yellow; purgation may be repeated. Senna is liable to cause pelvic congestion, therefore it is inadvisable in hæmorrhoids, pregnancy and menorrhagia.

Senna should be given with carminatives to alleviate griping; apart from this defect, it is a useful purgative, as its activity does not decrease with usage. Compound Liquorice Powder is a favourite purge for children; Syrup of Senna is less acceptable by them; the so-called "Syrup of Figs" is really a preparation of Senna. The Compound Mixture or "Black Draught" is an example of synergism, because the Senna stimulates the colon while the Magnesium Sulphate prevents absorption of water from the small intestine; it thus causes a copious liquid stool. It is used commonly to procure complete evacuation of the bowel in febrile illnesses, after anthelmintics, and to complete the action of mercurial purgatives.

Absorbed chrysophanic acid during excretion stains the urine brownish, or, if alkaline, red.

Phenolphthaleinum.—Phenolphthalein. Dihydroxy-diphenyl-phthalide $(C_6H_4OH)_2CO{\cdot}C_6H_4CO$. "Purgen."

CHARACTERS.—A white, tasteless, crystalline or amorphous powder. *Solubility.*—Insoluble in water, soluble in alcohol 90%; forms an intensely red colour with solutions of alkalis.

Dose.—Metric, 60 to 300 mg; Imperial, 1 to 5 gr.

Preparation

Tabellæ Phenolphthaleini.—0·12 G (2 gr.) in each.

ACTIONS AND USES

Phenolphthalein is a mild **purgative**; its formula is allied to that of anthraquinone. It dissolves in the alkaline contents of the intestine, is irritant to the mucous membrane, and appears to act mainly on the large intestine, where it increases peristalsis. A soft evacuation results without pain or griping in about six to eight hours. Some of the drug is absorbed; part is excreted in the urine, which, if alkaline, turns carmine; the bulk is excreted in the bile, hence a laxative effect persists for a day or so. Phenolphthalein is best given in the form of tablets. It is useful for weakly individuals and children suffering from chronic constipation; and may be given safely during pregnancy and in hæmorrhoids. Occasionally, it causes a pink or purplish macular skin eruption.

4. PURGATIVES ACTING ON BOTH SMALL AND LARGE INTESTINES

Hydragogue Purgatives cause evacuation of the bowels by irritating the mucous membrane and so increasing peristalsis in the small and large intestine that little time is allowed for the absorption of water. They cause a copious watery stool, accompanied by griping pain; the action may be repeated and associated with straining (drastic purgatives). Their active principles are glycosidal resins which are emulsified by the bile.

Ipomœa.—Ipomœa. Orizaba Jalap or Mexican Scammony Root. The dried root of Ipomœa orizabensis. N.O. Convolvulaceæ.

CHARACTERS.—Irregular, fibrous portions of greyish-brown roots. Slight odour. Taste faintly acrid.

COMPOSITION.—Ipomœa contains from 10 to 20% of a *glycosidal resin*, with fatty acids, starch, etc.

Preparation

Ipomœæ Resina.—Ipomœa Resin. Scammony Resin. A mixture of resins obtained by extracting Ipomœa with 90% Alcohol.

CHARACTERS.—Brownish, translucent, brittle fragments; resinous in fracture; odour characteristic, agreeable; taste acrid. Powder pale brown. Insoluble in water; soluble in alcohol 90%, and in ether.

COMPOSITION.—A glycosidal resin which hydrolyses into jalapinolic acid, $C_{15}H_{30}O_3$, and its methyl ester and dextrose.

Dose.—Metric, 30 to 200 mg; Imperial, 1/2 to 3 gr.

ACTIONS AND USES

Ipomœa Resin acts as a **hydragogue purgative**; its action is somewhat drastic and depends upon the emulsification of the resin by the bile. It produces copious liquid stools in from three to six hours, accompanied by considerable griping, and, in large doses, possibly inflammatory catarrh.

Ipomœa Resin is employed as a rapid purgative, chiefly to remove toxic or indigestible materials, or to drain off fluid in œdema. It is occasionally useful as a vermifuge for threadworms, and combined with Santonin, or following it, for roundworms.

Jalap.—(*Not official*) from Ipomœa purga also contains glycosidal resins. It is used as **Pulvis Jalapæ Compositus,** which is Powdered Jalap 30, Potassium Tartrate 60 and Ginger 10. *Dose.*—0·6 to 4 G (10 to 60 gr.). This increases peristalsis in both the small and large intestine and produces a liquid stool in two to six hours with griping. In the Compound Jalap Powder, the Acid Potassium Tartrate acts also as a saline purgative while the Ginger is carminative. It is sometimes used as a rapid evacuant and for dehydration in œdemas.

Kaladana, the seeds of Ipomœa hederacea. *Dose.*—2 to 3 G (30 to 45 gr.), and **Turpethum,** the dried root and stem of Ipomœa turpethum. *Dose.*—0·3 to 1·2 G (5 to 20 gr.). Both act like Jalap and are used in India and the Eastern Colonies.

Colocynthis.—Colocynth. The dried pulp of the fruit of Citrullus Colocynthis. N.O. Cucurbitaceæ, almost free from pericarp and seeds.

CHARACTERS.—White, spongy, light fragments. No odour; taste intensely bitter.

COMPOSITION.—Amorphous purgative *resins*; a bitter purgative glycoside, *colocynthin*; an amorphous purgative alkaloid, *colocynthine*; and *a-elaterin*, *citrullol*, etc., which are inactive.

Preparations

1. **Extractum Colocynthidis Compositum.**—Colocynth, Aloes, Ipomœa Resin, Curd Soap, and Cardamom Seed extracted with Alcohol 60% and evaporated to dryness.
Dose.—Metric, 0·12 to 0·5 G; Imperial, 2 to 8 gr.
2. **Pilula Colocynthidis et Hyoscyami.**—Colocynth 12·5%, Aloes and Ipomœa Resin, each 25%, Dry Extract of Hyoscyamus, 12·5%, with Curd Soap, Oil of Clove and Syrup of Liquid Glucose.
Dose.—Metric, 0·25 to 0·5 G; Imperial, 4 to 8 gr.

ACTIONS AND USES

Colocynth is a powerful **gastro-intestinal irritant,** and may give rise to nausea or vomiting. Its typical irritant effects are developed in the intestine, where it increases the mucous secretions of the bowel and greatly accelerates peristalsis, causing considerable griping pain, unless combined with carminatives or Atropine (e.g. Hyoscyamus Extract) to check spasmodic contractions. It is one of the most powerful **hydragogues,** producing repeated and copious watery evacuations in two or three hours. In large doses it may cause intestinal catarrh and inflammation.

Colocynth is never prescribed alone, but with milder purgatives and carminatives. The Pill of Colocynth and Hyoscyamus is given as a purgative in obstinate constipation, and it may be used for severe constipation during pregnancy.

Podophyllum.—Podophyllum Rhizome. The dried rhizome and roots of Podophyllum peltatum. N.O. Berberideæ.

CHARACTERS.—A reddish-brown rhizome of variable length, showing at intervals enlargements, with a depressed circular scar above and brown roots below; section, white and starchy. Odour characteristic; taste slightly bitter and acrid.

COMPOSITION.—Podophyllum contains the official *resin,* which yields 1% *podophyllotoxin,* $C_{15}H_{14}O_6$, a neutral crystalline glycoside hydrolysing into podophyllic acid; and *podophylloresin*; both are purgative. *Picropodophyllin* and *quercetin* are also present.

Podophyllum Indicum.—Indian Podophyllum Rhizome. The dried rhizome and roots of Podophyllum hexandrum.

CHARACTERS.—Brown, tortuous, flattened rhizomes, showing scars of stems and roots; section, pale brown, starchy. Odour slight; taste bitter, acrid.

COMPOSITION.—Contains about twice as much *podophyllotoxin* (2 to 5%) and *podophylloresin* as Podophyllum Rhizome.

Dose of both.—Metric, 0·12 to 0·6 G; Imperial, 2 to 10 gr.

Preparation

Podophylli Resina.—Podophyllum Resin. A mixture of resins, obtained from Podophyllum, or Indian Podophyllum.

CHARACTERS.—A yellow amorphous powder; insoluble in water.

COMPOSITION.—*Podophyllotoxin* 20% (Indian 40%) and *podophylloresin.*

Dose.—Metric, 15 to 60 mg; Imperial, 1/4 to 1 gr.

ACTIONS AND USES

Internally.—Podophyllum Resin has a bitter acrid taste, and may cause nausea. In the intestine the Resin is emulsified by the bile, and then exerts its irritant effects, causing violent peristaltic contractions accompanied by severe griping, and increasing the intestinal mucous secretions. Podophyllum acts slowly, in from ten to twelve hours, but it is distinctly a **drastic purgative**, causing a complete watery evacuation of the bowel. Its repute as a "cholagogue" is unmerited.

Podophyllum is used as a purgative in severe constipation, and to remove intestinal parasites. Doses of 1/8 to 1/4 gr. of the Resin may be employed in laxative pills; it should be combined with Dry Extract of Hyoscyamus or of Belladonna to counteract the excessive griping.

Oleum Crotonis (*not official*).—Croton Oil. The oil from the seeds of Croton Tiglium. N.O. Euphorbiaceæ, is brownish-yellow, has a disagreeable odour, and, cautiously tasted, is acrid. The active principle is an irritant vesicant lactone, *croton resin*, $C_{13}H_{18}O_4$, dissolved in various fixed oils.

Dose.—Metric, 0·03 to 0·06 Mil; Imperial, 1/2 to 1 min.

ACTIONS AND USES

Externally.—Croton Oil is a **vesicant** and, on skin in 10 per cent. solution, it causes burning pain and papules, which coalesce into pustules, around the sweat glands.

Internally.—Croton Oil is the most **drastic purgative**. The irritant croton resin produces sensations of burning in the throat and epigastrium with nausea and perhaps vomiting; in the intestine the severe irritation leads to greatly augmented peristalsis and acute catarrh of the mucous membrane. Purgation occurs very rapidly, in one to two hours, of a copious semi-solid stool, accompanied by griping; several watery evacuations with severe straining generally follow. Croton Oil should not be used except for insane patients, to whom, owing to its small dose, it can be given in a little butter.

Croton Seeds, but not the Oil, contain a toxalbumose, *Crotin*, which agglutinates blood-corpuscles, like Ricin.

IX.—Cholagogues

Cholagogues are drugs which increase the amount of bile secreted by the liver (*Direct Cholagogues*). The salts of the bile are the most effective but the secretion is increased in less degree by Cinchophen, Phenolphthalein, Salicylates and Benzoates. *Indirect Cholagogues* are drugs which cause evacuation of the gall bladder, the most efficient are fatty foods, especially cream and egg-yolk, or fixed oils, e.g. Olive and Castor Oils. Hypertonic solutions of Magnesium or Sodium Sulphate in the duodenum also evacuate the gall bladder. Calomel and other purgatives which cause the appearance of undecomposed bile pigments in the stools are incorrectly termed cholagogues.

Extractum Fellis Bovini.—Purified Ox Bile. Extract of Ox Bile.

SOURCE.—Prepared from fresh ox bile by evaporation and precipitation of mucus, etc., by Alcohol 90%.

CHARACTERS.—A yellowish-green, hygroscopic, soft extract; taste unpleasant, bitter. *Soluble* in water.

COMPOSITION.—Extract of Ox Bile contains the bile salts *sodium glycocholate* and *sodium taurocholate* and the bile pigments *bilirubin* and *biliverdin;* free from mucus.

Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

ACTIONS AND USES

The physiological actions of Bile are dependent largely on the property of the bile salts in lowering surface tension; thus Bile accelerates the hydrolysis of fats by lipase, promotes soap formation, and facilitates the absorption of fats by the intestine. Bile salts also emulsify the glycosidal resinous purgatives. Ingestion of bile salts actively **stimulates the secretion of bile,** the taurocholates being more active than the glycocholates.

Extract of Bile may be given when excess of fats in the fæces indicates defective duodenal digestion and absorption of fats, but it should be given in capsules or pills coated so that they may pass through the stomach. It has also been given, because it stimulates the large intestine, as a purgative in intestinal atony by mouth or as an enema (1 : 50); the latter is useful to remove threadworms.

X.—VEGETABLE ASTRINGENTS

The vegetable astringents owe their value to Tannic Acid, which acts by precipitating proteins.

Acidum Tannicum.—Tannic Acid. Tannin.

SOURCE.—Extracted by water-saturated ether from oak Galls, subjected to a special fermentation.

CHARACTERS.—Light-brownish, glistening scales or powder; odour characteristic; taste strongly astringent; reaction acid. *Solubility.*—1 in 1 of water; 1 slowly in 1 of glycerin. *Incompatibles.*—Gelatin mineral acids; alkalis; salts of heavy metals; ferric salts, giving a bluish-black colour; most alkaloids.

Preparations

1. **Glycerinum Acidi Tannici.**—15% in Glycerin.
2. **Suppositoria Acidi Tannici.**—0·2 G (3 gr.) in each, with Oil of Theobroma.
3. **Trochisci Acidi Tannici.**—30 mg (1/2 gr.); with Lozenge Basis.

ACTIONS AND USES

The principal action of Tannic Acid is **astringent**: it diminishes the secretions of living tissues by precipitating the proteins in superficial cells: if Tannic Acid be neutralized by alkali or by albumin its astringency is lost.

Externally.—Tannic Acid is not an antiseptic, but its albuminous precipitate resists micro-organismal growth. Its solutions will harden and roughen the skin, and check excessive sweating. If applied to a raw surface or to mucous membranes, it **precipitates the superficial proteins**, and forms a protective coating for the tissues beneath; on wounds, it checks exudation of serum or lymph and retards inflammation. On mucous membranes it also reduces mucous secretions and exudations from the superficial cells and glands. Stronger solutions act as **styptics or hæmostatics** by precipitating the proteins of the blood.

Tannic Acid is applied locally to wounds, ulcers and bleeding surfaces, in the form of dusting powders, ointments (10 per cent.), pastes or lotions (5 per cent.). It is most useful where there is excessive secretion, as in weeping ulcers. It is also used as a dusting powder or the Glycerin to check perspiration; and in solutions (5 per cent.) to prevent bed-sores and blistering of the feet;

to reduce exudation in intertrigo and other affections of the skin, and to harden sore nipples. Bougies or injections are employed in urethritis and leucorrhœa. The Suppositories are used for hæmorrhoids.

Tannic Acid (2 to 5 per cent.) in water may be used in the **treatment of burns**; the warmed solution is sprayed every half-hour over the burned area, and dried. The brown protein precipitate, by preventing absorption of toxins, lessens shock, diminishes acute toxæmia, and allays pain. It loosens in about a week and may require to be re-applied. Fresh solutions of Tannic Acid must be used, as they decompose in a day or two. Tannic Acid should not be used for burns of the face or hands because contracture of the scars may leave unsightly blemishes or impaired function, nor for large burns because absorption of Tannic Acid may cause liver necrosis.

Internally.—When Tannic Acid is applied to the mouth or throat, a sensation of dryness, thirst and constriction of the parts is noticed; the secretions are checked. Tannic Acid is a valuable **astringent** for swollen, tender or bleeding gums, and for tonsillitis, sore throat and pharyngitis, in the form of gargles (1 to 5 per cent.), of paints, e.g. the Glycerin (diluted with 8 of water) or of the Lozenge. In nasal catarrh and bleeding, a douche (1 per cent.) or a snuff containing Tannic Acid is useful.

In the *stomach*, Tannic Acid precipitates the proteins of the food as tannates; these are digested, and as peptone does not unite with Tannic Acid, the Acid is again liberated. If little food be present, the astringent action is exerted on the gastric walls. Small doses are sometimes useful in chronic catarrhal gastritis to reduce mucous secretion and as hæmostatics in chronic gastritis or ulcer. Large doses cause indigestion both by precipitation of food and by reducing gastric secretion. Tannic Acid is also an important **antidote** in poisoning from heavy metallic salts and alkaloids; but it should be followed by an emetic and a purge.

In the *intestine* the astringent action of pure Tannic Acid is soon lost, because the alkaline contents convert it into tannates or gallates, which have no astringency. The **astringent effect** in the bowel can be attained by using the **crude drugs**, e.g. Catechu, Kino, Krameria, which liberate Tannic Acid in the intestine slowly as they are being broken up. This Tannic Acid precipitates undigested food proteins, so rendering the contents more solid, and also proteins in the mucosa, so forming a protective coating which diminishes peristalsis. These effects lead to delayed transmission of the intestinal contents, so that more water is absorbed from the fæces and **constipation results.**

Tannic Acid and the vegetable drugs that contain it are used in the treatment of persistent diarrhœa, particularly when this is due to subacute or chronic inflammation with much mucous secretion. In such cases they are suitably given with Bismuth, Chalk or Opium. Combined with Opium they are also of service in intestinal hæmorrhage. Since Tannic Acid cannot reach the colon in active condition when given by the mouth, it has been employed as an enema in colitis, cholera and dysentery.

Alkali tannates and gallates are absorbed, and partly excreted in the urine or undergo complete oxidation. They exert no remote astringent actions.

Catechu.—Catechu. Pale Catechu. A dried aqueous extract of the leaves and shoots of Uncaria Gambier. N.O. Rubiaceæ.

CHARACTERS.—Dark reddish-brown, friable cubes, consisting of minute acicular crystals. No odour; taste bitter, very astringent, then sweetish. *Solubility.*—Almost entirely in boiling water, and in alcohol 90%.

COMPOSITION.—Catechu contains 22 to 50% of *catechu-tannic acid,* the active principle; a crystalline, bitter substance, *catechin* or *catechuic acid,* $C_{15}H_{14}O_6,4H_2O$, probably inactive; *catechu-red,* $C_{36}H_{34}O_{15}$; and *gambier-fluorescein.*

Preparation

Tinctura Catechu.—Catechu 20% with Cinnamon in Alcohol 45%. **Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.**

ACTIONS AND USES

Catechu acts like Tannic Acid. The powdered drug, because its Tannic Acid is released slowly, is used (5 to 15 gr.) as an **intestinal astringent** in diarrhœa, sometimes with powdered Cinnamon as a carminative. The Tincture is astringent in the mouth and is used (1 in 50 of water) to treat inflammation of mucous membranes of the mouth and throat.

Krameria.—Krameria Root. Rhatany Root. The dried root of Krameria triandra (Peruvian Rhatany). N.O. Polygaleæ.

CHARACTERS.—Tortuous reddish-brown roots with scaly bark and paler wood. Odourless; taste of bark astringent, of wood scarcely perceptible.

COMPOSITION.—Krameria Root contains from 8 to 10% of *krameria-tannic acid,* a red amorphous substance; *krameria-red*; and starch. **Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.**

Preparations

1. **Extractum Krameriæ Siccum.**—Dried aqueous extract.
Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.
2. **Trochisci Krameriæ.**—60 mg (1 gr.) of Extract with Lozenge Basis.
3. **Trochisci Krameriæ et Cocainæ.**—60 mg (1 gr.) of Extract and 3 mg (1/20 gr.) of Cocaine Hydrochloride, with Lozenge Basis.

ACTIONS AND USES

Krameria preparations are **typical astringents**; the Extract and powdered Krameria are intestinal astringents given in pill form; the Trochisci for laryngitis.

Kino (*not official*).—Kino. The evaporated juice obtained from the trunk of Pterocarpus Marsupium. N.O. Leguminosæ. Occurs as small, reddish-black, brittle fragments; taste very astringent, tinging saliva red. *Solubility.*—Partially in water.

COMPOSITION.—Kino contains 75% of *kino-tannic acid*; *pyrocatechin*; *kino-red*, and *gum*.
Dose.—In powder: Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

ACTIONS AND USES

Kino acts like Tannic Acid but its **astringency persists longer in the bowel. Pulvis Kino Compositus** (B.P. 1914), which contains Kino, 75, Opium, 5, Cinnamon, 20, *Dose.*—0·3 to 1·2 G (5 to 20 gr.), is used very frequently for diarrhœa; the Opium diminishes peristalsis.

Hamamelis.—Hamamelis Leaves. Witch Hazel Leaves. The dried leaves of Hamamelis virginiana. N.O. Hamamelidaceæ.

CHARACTERS.—Dark-green, broadly oval, petiolate leaves, veins pinnate, undersurface shows stellate hairs. Odour not marked; taste astringent, slightly bitter.
COMPOSITION.—The leaves contain *tannic acid*; *gallic acid*; a bitter principle; and volatile oil.

Preparations

1. **Extractum Hamamelidis Liquidum.**—1 in 1 of Alcohol 45%.
2. **Extractum Hamamelidis Siccum.**—A dry Extract.
3. **Unguentum Hamamelidis.**—10% in Wool Fat and Yellow Soft Paraffin.
4. **Suppositoria Hamamelidis.**—Dry Extract, 0·2 G (3 gr.), in Oil of Theobroma.
5. **Suppositoria Hamamelidis et Zinci Oxidi.**—Dry Extract, 0·2 G (3 gr.), with 0·6 G (10 gr.) Zinc Oxide in Oil of Theobroma.

ACTIONS AND USES

The Liquid Extract, 5 per cent. in water, is used as a local astringent, or 10 per cent. in ointment bases as an application for hæmorrhoids; the Dry Extract in the Suppositories is similarly a mild astringent. Hamamelis is contained in many proprietary cosmetics.

XI.—ANTHELMINTICS

Anthelmintics are drugs which either kill or remove parasitic worms infesting the intestinal canal. They are also termed *Vermicides*, which kill the worm; and *Vermifuges*, which expel the worm but do not kill it; these latter are mainly purgatives.

Filix-Mas.—Male Fern. The rhizome of Dryopteris Filix-mas. N.O. Filicineæ.

CHARACTERS.—Dark-brown rhizome, covered with bases of petioles, bearing scales; internally green. Odour feeble but disagreeable; taste sweetish and astringent at first, subsequently bitter and nauseous.

COMPOSITION.—Male Fern contains a yellow amorphous acid principle *filmarone*; it decomposes into *filicic acid*, and *aspidinol*. *Albaspidin*, *filicitannic acid*, and *fixed oil* are also present. Filicin is an ether-soluble lactone of filicic acid.

Preparation

Extractum Filicis.—Extract of Male Fern. An oily extract made by percolating with solvent ether, and then evaporating or distilling off the ether. *Standardized* to contain 25% of Filicin.
Dose.—Metric, 3 to 6 Mils; Imperial, 45 to 90 min.

ACTIONS AND USES

Male Fern is used solely as an **anthelmintic**. It is directly toxic—*vermicidal*—to tapeworms, and is used to remove Tænia solium, Tænia saginata (mediocanellata) and Dibothriocephalus latus, and also hookworms (Ankylostoma duodenale). The Extract is best given emulsified with an equal weight of Gum Acacia, and strongly flavoured, e.g. with Cinnamon or Ginger, as its taste is very nauseating; or it may be prescribed as a Capsule (B.P.C.). The patient is allowed very little, but easily absorbed, food for two days and given each day a large dose of a Saline Purgative in order to empty the bowel; early on the third morning the Extractum Filicis is given and two hours later a third purgative dose of Magnesium Sulphate to remove the worm and prevent absorption of the Male Fern. Castor Oil, which dissolves filicic acid and aids its absorption, should be avoided. If the head of the worm is not found in the stool, treatment should not be repeated until a week has elapsed, as Male Fern is a *cumulative poison*.

The toxic effects are gastro-enteritis, with vomiting and diarrhœa, headache, muscular weakness, twitching and increased reflex excitability or even convulsions; visual impairment or temporary blindness frequently occurs.

Pelletierinæ Tannas.—Pelletierine Tannate. A mixture of the tannates of the alkaloids obtained from the bark of the stem and root of the Punica Granatum, the Pomegranate. N.O. Lythrarieæ.

CHARACTERS.—A light-yellow, amorphous powder. *Solubility.*—Slightly in water. No odour; taste astringent.
COMPOSITION.—Pomegranate Bark contains three liquid alkaloids—*pelletierine*, or *punicine*, $C_8H_{15}NO$, *isopelletierine*, and *methylpelletierine*, $C_9H_{17}NO$; and a crystalline alkaloid, *pseudo-pelletierine*, $C_9H_{15}NO,2H_2O$; also *punicotannic acid*.
Dose.—Metric, 0·12 to 0·5 G; Imperial, 2 to 8 gr.

ACTIONS AND USES

Pelletierine in strengths of 1 to 5,000 is **vermicidal** to tapeworms but not to roundworms. The tannate is used because it is insoluble in the stomach; in the intestine the alkalinity liberates the alkaloids. The patient is prepared as for Male Fern and Pelletierine Tannate is given suspended in water, on an empty stomach, and is followed by a saline purgative in an hour or two. When absorption occurs, weakness in the limbs, giddiness and dimness of vision are observed.

Santoninum.—Santonin. $C_{15}H_{18}O_3$. A crystalline lactone of santonic acid, obtained from the flower-heads of Artemisia cina. N.O. Compositæ.

CHARACTERS.—Colourless, flat prisms or powder; sunlight renders it yellow; odourless, taste slightly bitter. *Solubility.*—Scarcely in water; readily in dilute alkalis.
Dose.—Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

ACTIONS AND USES

Santonin is used as an **anthelmintic for the roundworm** (Ascaris lumbricoides) which lives in the small intestine. It does not usually kill the parasites; it is obnoxious to them and directly stimulates their musculature, causing active movements which detach the parasites' hold so that they are easily expelled by the subsequent purgative. Santonin is usually given as a lozenge or a powder mixed with sugar, either as a single dose or in three doses at hourly intervals followed at once by Calomel and two hours later by a saline purgative. Previous starvation is inadvisable as this favours absorption, as also does Castor Oil. The threadworm Oxyuris vermicularis is not easily removed by Santonin, and this drug has no influence on tapeworms.

Santonin, which forms sodium santoninate in the intestine, is absorbed and gives rise to peculiar symptoms. One of the earliest of these is a **disturbance of vision**, objects appearing first blue, then yellow (chromatopsia or xanthopsia), followed occasionally by violet vision, and recovery in a few hours. The xanthopsia is due to some specific effect on the retina and, to avoid the alarm it causes, the Santonin can be given at bed-time, and the purgative early next morning. With large doses, twitching and tremors of muscles, followed by epileptiform and clonic spasms, develop from an action of the naphthalene nucleus on the cerebrum; the medullary centres are little affected. Santonin is excreted in the urine and fæces as oxysantonin, giving these an orange colour, which changes to pink on addition of alkali.

Oleum Chenopodii.—Oil of Chenopodium. Oil of American Wormseed. The oil distilled from fresh flowering and fruiting plants of Chenopodium ambrosioides, var. anthelminticum. N.O. Compositæ.

COMPOSITION.—Contains not less than 65% of *ascaridole*, $C_{10}H_{16}O_2$, with *terpenes*.

Dose.—Metric, 0·2 to 1 Mil; Imperial, 3 to 15 min.

ACTIONS AND USES

Oil of Chenopodium is **anthelmintic** to the roundworm (Ascaris), and hookworms (Ankylostoma duodenale and Necator americanus); it appears to cause stimulation followed by paralysis of the roundworm. A purgative, such as Magnesium Sulphate or Castor Oil, must be given later because the volatile Oil of Chenopodium checks intestinal peristalsis. Oil of Chenopodium may be given mixed with sugar or in a gelatin capsule; for children the dose of 1 min. for each year of life is suitable. Previous starvation or purgation is not required.

For the removal of roundworms and threadworms, a single dose of 0·6 Mil (10 min.) is given in the morning and followed in two hours by a saline purgative or Castor Oil.

In **hookworm infections,** Oil of Chenopodium is generally more effective than Thymol and more easily taken, and it is better for Ankylostoma than Carbon Tetrachloride with which it is commonly given. Without previous preparation, three doses of 0·5 to 1 Mil (8 to 15 min.) of the Oil are given at intervals of one or two hours; and two hours later Magnesium Sulphate or Castor Oil. Repetition of treatment, when necessary, should be postponed for at least a week. Oil of Chenopodium is also useful to remove amœbæ from the intestine, and is worthy of trial in dysentery which resists Emetine treatment.

Actions after absorption.—Slight symptoms of poisoning are not uncommon; they consist of giddiness, nausea or vomiting (often bloodstained), tingling sensations in the hands and feet and degrees of deafness. Excessive doses cause convulsions passing into coma.

Carbonei Tetrachloridum.—Carbon Tetrachloride. CCl_4.

CHARACTERS.—A colourless, volatile liquid; odour characteristic, taste burning. Insoluble in water.
Dose.—*Single:* **Metric, 2 to 4 Mils; Imperial, 30 to 60 min.**

ACTIONS AND USES

Externally.—Carbon Tetrachloride was used in "dry shampoos" but the inhalation of the vapour is dangerous and may cause narcosis and bronchitis.

Internally.—Carbon Tetrachloride is given by a single dose in milk or in a gelatin capsule, which must be swallowed whole. It is an anthelmintic for **hookworm infection** and is more effective for Necator than Oil of Chenopodium. The single dose is given in the morning and followed after two hours by Magnesium Sulphate; repetition should be postponed for a fortnight. Children tolerate about 2 min. for each year of age.

A mixture of Carbon Tetrachloride 2 or 3 with Chenopodium Oil 1 is often better, particularly for children, in doses of 0·1 Mil for each year of age up to 1·5 Mils, and appears to be more effective for Ankylostoma duodenale. It may be given in a capsule or diluted with Liquid Paraffin. This mixture is also recommended for tapeworm and roundworm.

Actions after absorption.—Absorption gives rise to severe headache and narcosis, and to fatty degeneration of the liver. Poisoning is avoidable if the patient is well nourished, refrains from alcohol and fatty foods but receives adequate protein, carbohydrate and calcium as protectives.

Tetrachloroæthylenum.—Tetrachlorethylene. C_2Cl_4.

CHARACTERS.—A colourless liquid; odour like Carbon Tetrachloride.
Dose.—*Single:* **Metric, 1 to 3 Mils; Imperial, 15 to 45 min.**

ACTIONS AND USES

Tetrachlorethylene is a more valuable anthelmintic for hookworms (Ankylostoma and Necator) and much less toxic than Carbon Tetrachloride, but it causes giddiness, hence patients should be recumbent; it does not injure the liver or kidneys. It is not reliable for other worms. Treatment consists in giving 3 Mils

(45 min.) in a gelatin capsule or in mixture with Oil of Chenopodium, and following this in two hours by a purgative dose of Sodium or Magnesium Sulphate. It is also used in trichinosis.

Thymol.—Thymol. $C_6H_3.CH_3.OH.C_3H_7$. A crystalline phenol, obtained from the volatile oils of Thymus vulgaris, Monarda punctata, and Trachyspermum Ammi, or prepared synthetically.

CHARACTERS.—Colourless crystals; odour pungent, like thyme; taste pungent, aromatic. *Solubility.*—1 in 1,000 of water; 1 in 1 of alcohol 90%.

Dose.—Metric, 30 to 120 mg; Imperial, 1/2 to 2 gr.

As an Anthelmintic:

Metric, 1 to 2 G; Imperial, 15 to 30 gr.

ACTIONS AND USES

Externally.—Thymol has much greater **antiseptic** powers than Phenol and is much less toxic to the tissues; it has a moderate surface anodyne action. Its insolubility in water restricts its use to that of antiseptic mouth-washes, gargles or sprays (1 : 1,000), e.g. in the form of the Glycerinum or Liquor Thymolis Co. (B.P.C.) for the treatment of oral and nasal infections; and as an ointment (4 per cent.) for itching skin diseases.

Internally.—Thymol is administered for the **removal of hookworms**; it is more toxic to the Necator americanus than to Ankylostoma duodenale; but not so effective as Tetrachlorethylene. The patient should receive no evening meal but a dose of Magnesium Sulphate to clear the intestine. Thymol is given in capsules in the morning either as a single dose of 2 to 3 G, or in divided doses, 1·3 G (20 gr.), at hourly intervals; two hours later Magnesium Sulphate (not Castor Oil) is given again. Treatment may be repeated weekly. Thymol is also effective for removing Ascaris lumbricoides.

Actions after absorption.—Thymol has only one-fourth the general toxicity of Phenol; about half is metabolized in the body, the rest is excreted as ethereal sulphates in the urine.

Diphenanum.—Diphenan. Butolan. *p*-benzylphenylcarbamate. $C_6H_4.CH_2.C_6H_5.OCO.NH_2$.

CHARACTERS.—A white or cream, tasteless, crystalline powder; almost insoluble in water.

Dose.—Metric, 0·5 to 1 G; Imperial, 8 to 15 gr.

ACTIONS AND USES

Diphenan is toxic to **threadworms** but not to their ova. It is given in tablets (0·5 G) thrice daily for a week but the course should be repeated after a week's interval in order to kill worms developed from residual ova. From 1/4 to 1/2 the adult dose is used for children, who must be prevented from reinfecting themselves through anal scratching, and the anal region should be anointed with Ammoniated Mercury Ointment.

Viola Crystallina.—Crystal or Gentian Violet. The hydrochloride of hexamethylpararosaniline.

CHARACTERS.—A greenish-bronze powder or crystals. Solubility, 1 in 150 of water.

Dose (*not official*).—

Adults: **Metric, 30 to 60 mg ; Imperial, 1/2 to 1 gr. thrice daily.**
Children: **3 mg (1/20 gr.) for each year of age thrice daily.**

ACTIONS AND USES

Externally.—Gentian Violet is an antiseptic, effective against Gram-positive organisms and not irritant. In aqueous (0·5 to 1 per cent.) solutions it is used as a **skin antiseptic**, usually along with the same strength of Brilliant Green, for sensitive skin areas, e.g. perineal region, and for application to septic skin eruptions, boils and carbuncles. Gentian Violet in 1 or 2 per cent. solution is also painted on impetigo contagiosa, sycosis and ringworm. As **"Triple Dye"** (Gentian Violet 1 gr., Brilliant Green 1 gr., and Proflavine Hemisulphate 1/2 gr. per fl. oz.), it is employed in the treatment of superficial burns, over which it forms a pliable pellicle which resists infection.

Internally.—Gentian Violet is the usual anthelmintic employed to **remove threadworms**, and it is given in enteric-coated pills. For adults, 60 mg (1 gr.) are given thrice daily for a week; but for children, 10 mg (1/6 gr.) daily for each year of life are used divided into three equal doses. The pills are taken before meals. In adults some nausea and diarrhœa may occur. Protective measures against reinfection are mentioned above. Gentian Violet is also effective for removing liver flukes.

Hexyl-Resorcinol (*see* p. 373) is also used as an anthelmintic for round-, thread-, hook- and tapeworm infections.

Phenothiazine.—Phenovis. A lemon-yellow thiazine dye, which, although toxic to round- and threadworms, is also very toxic to man, causing vomiting, jaundice and acute hæmolytic anæmia. It is not used for human treatment.

XII.—INTESTINAL ANTISEPTICS—ADSORPTIVE AGENTS

Formerly, Phenol compounds—Phenol, Salol, Thymol, etc., and Mercurial Preparations—Calomel, Mercury with Chalk, and

Mercuric Chloride—in small doses were used largely as intestinal antiseptics. They have been displaced by the less absorbable sulphonamides—Sulphaguanidine, Succinylsulphathiazole and Phthalylsulphathiazole (*see* p. 408).

Insoluble amorphous powders are capable of **adsorbing toxins.** This property is possessed in high degree by **Carbo,** Charcoal, *Dose.*—4 to 8 G (60 to 120 gr.), which adsorbs alkaloids, pigments, and gases, and can be administered in the form of lozenges or biscuits. Light Kaolin and Bismuth salts, and to a lesser degree the insoluble Calcium and Magnesium salts, also act as adsorbents. It is partly to these powers of adsorbing toxins that these substances owe their value in the treatment of bacterial diarrhœas and cholera.

XIII.—INTESTINAL SEDATIVES

A sedative action on the intestine may be produced by: (1) **Mechanical Protectives,** which protect the intestinal mucosa from irritation by forming a coating over it, e.g. Bismuth salts, Light Kaolin, or insoluble Calcium salts; astringents, both metallic and vegetable, by precipitating the epithelial proteins, have a similar action. (2) **Carminatives** (volatile oils), which relax spasmodic contractions in the intestine and allay griping. (3) **Depressants of the Vagal Endings,** e.g. Atropine, Belladonna, Hyoscyamus, which check spasmodic contractions. (4) **Depressants of the muscular movements,** e.g. Opium, Papaverine and Pethidine, which cause quiescence of the intestine.

XIV.—VITAMINS AND NUTRIENT MATERIALS

Many food substances are valuable because they contain nutrient materials in easily assimilated form, while some contain vitamins, which are essential for the growth and health of the organism.

Vitamins.—It is now known that, although a diet may be perfectly balanced and contain an adequate amount of proteins, carbohydrates and fats, it may still fail to promote growth or calcification of bones, or may cause diseases such as scurvy, beri-beri or pellagra. In such conditions, which are spoken of as "deficiency diseases," there is lacking from the diet organic compounds termed "accessory food factors" or vitamins, which in minute amounts are prophylactic against and curative in those diseases.

VITAMIN A.—Growth and Epithelial Factor (Fat Soluble).

Sources.—Vitamin A is derived by animals from plant pigments, namely, from α-, β-, and γ-carotene and cryptoxanthine, which occur in green vegetables and carrots; but animals concentrate this vitamin in their fatty tissues, hence it is found richly in whole milk, cream, butter, egg yolk, cod-liver oil, and halibut-liver oil; and in the viscera of fishes, and in spinach. It is absent from lard and vegetable fats.

Oleum Hippoglossi.—Halibut-liver Oil. A fixed oil expressed from the fresh, or suitably preserved, liver of Hippoglossus hippoglossus. 1 G contains not less than 30,000 Units of Vitamin A activity.

CHARACTERS.—A yellow, oily liquid, with fishy taste and smell.
Dose.—*Daily.* 1,500 *to* 12,000 *Units.*
Metric, 0·06 to 0·5 Mils; Imperial, 1 to 8 min.

Preparations

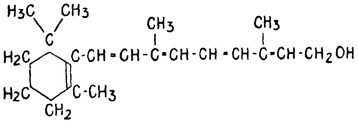
1. **Liquor Vitaminini A Concentratus.**—Concentrated Solution of Vitamin A. 1 G contains 50,000 Units of Vitamin A activity and *not more* than 500 Units of Vitamin D.

CHARACTERS.—A yellow, oily liquid, either a fish-liver oil, or a source of Vitamin A in a suitable vegetable oil, e.g. Arachis.
Dose.—*Daily.* 2,500 *to* 25,000 *Units.*
Metric, 0·06 to 0·6 Mil; Imperial, 1 to 10 min.

2. **Liquor Vitaminorum A et D Concentratus.**—Concentrated Solution of Vitamins A and D. 1 G contains 50,000 Units of Vitamin A and 5,000 Units of Vitamin D activity.

CHARACTERS.—A yellow, oily liquid, either a fish-liver oil, or sources of Vitamins A and D in a suitable vegetable oil, e.g. Arachis.
Dose.—*Daily.* 2,500 *to* 25,000 *Units of A, and* 250 *to* 2,500 *Units of D.*
Metric, 0·06 to 0·6 Mil; Imperial, 1 to 10 min.

Composition.—It is a complex alcohol formed chiefly from the lipochrome, β-carotene, by the liver, which hydrolyses the β-carotene molecule into two of Vitamin A. It is stable to heat but readily destroyed by acids, oxidizing agents (when impure), or ultra-violet light.



. Vitamin A

Standard for Vitamin A.—The International Unit is the specific activity contained in 0 6 microgram (0·6γ) of the Standard Preparation of pure β-carotene. In litters of rats deprived of Vitamin A for four weeks, 1 to 3 Units per rat per day are given and the weekly weight increases for three weeks compared with those produced by equal doses of the Standard Preparation. Solutions of Vitamin A in alcohol or cyclohexane exhibit an absorption band in the ultra-violet spectrum at 328 mμ, which is proportional in intensity to the Vitamin A content of the solution. A saturated solution of antimony trichloride in dry chloroform gives with solutions of 0·04 G Vitamin A in chloroform a blue colour, the depth of which indicates approximately the amount of Vitamin A.

Symptoms of Deficiency.—Deprivation of Vitamin A produces (1) stoppage of growth and flattening of the weight curve in young animals; (2) slow regeneration of the visual purple, rhodopsin, and so the production of night blindness; (3) stratified keratinization of the epithelium in the mucous membranes of the nose, trachea, and bronchi; (4) atrophy of the cells of the salivary glands, the mucous glands of the intestine and of the intestinal villi; (5) imperfect development of the periodontal tissues; (6) dryness of the skin and liability to papular eruptions; (7) xerophthalmia or keratomalacia, exhibited by a purulent conjunctivitis with corneal thickening and ulceration. Great deficiency may cause demyelination of nerves, formation of phosphatic calculi and defects in bone and enamel structure.

Animals deprived of Vitamin A not only cease to grow or increase in weight but also become more susceptible to bacterial infections, owing to the degenerative changes in the epithelial protective membranes of the body.

ACTIONS AND USES

Vitamin A is necessary for proper growth of the young and for maintaining the normal histological structure of the epithelial tissues in the body, and thus of preserving their resistance against invasion by bacteria, and for the regeneration of rhodopsin. But its administration in large doses neither increases normal growth, nor increases resistance to bacterial infections, nor accelerates recovery from bacterial invasion of mucous membranes, or of the body, in persons who are on a normal dietary. The daily requirements are 15 to 30 Units per Kg. body weight, or the adult prophylactic dose is 1,000 to 2,000 Units; and if a diet deficient in Vitamin A has been the cause of night blindness, periodontal diseases, or recurrent infections, then the administration of Vitamin A will be beneficial, if not always curative.

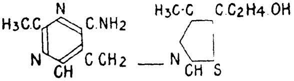
VITAMIN B.—A Complex Group of Factors (Water Soluble).

Source.—Vitamin B factors are richly available in the germ and outer layers of cereals and legumens, in yeast and nuts, but are also present in vegetables, fruits, egg yolk, milk, and meat. They are absent from white but present in wholemeal bread.

Aneurinæ Hydrochloridum.—Aneurine Hydrochloride. Vitamin B_1. Thiamine Hydrochloride. Obtained from rice polishings, yeast, other natural sources, or by synthesis.

CHARACTERS.—Colourless, plate-like, soluble crystals, taste bitter.

COMPOSITION.—Aneurine is a pyramidine-thiazole compound. It is stable at 100° C., not oxidized in air but is destroyed by its alkalis.



Aneurine

Dose.—*Prophylactic (daily):*
Metric, 1 to 3 mg; Imperial, 1/60 to 1/20 gr.
Therapeutic (daily):
Metric, 10 to 30 mg; Imperial, 1/6 to 1/2 gr.

Preparations

1. **Injectio Aneurinæ Hydrochloridi.**—A sterile Solution in Water for Subcutaneous or Intramuscular Injection. Contains 25 mg (2/5 gr.) in 1 Mil (15 min.).
2. **Tabellæ Aneurinæ Hydrochloridi.**—1 mg (1/60 gr.) in each.

Symptoms of Deficiency.—In man, lack of Aneurine results in loss of appetite, fatigue, apathy, nausea, polyneuritis shown by impaired sensation with muscular pains and weakness, tachycardia and low blood-pressure.

In man, prolonged deficiency of Aneurine, but also of other factors, **causes beri-beri**, in which loss of appetite, epigastric pain, and constipation, along with dyspnœa, cardiac weakness, low blood-pressure, and a weak, rapid pulse, are followed by œdema and multiple peripheral neuritis of both sensory and motor types. The daily requirements in adults is about 1 to 2 mg.

ACTIONS AND USES

The pyrophosphoric ester of Aneurine is a co-enzyme of carboxylase and one of its actions is the decarboxylation of pyruvic and lactic acids. In its absence, pyruvic acid—and also lactic acid—accumulate in the blood, as is the case in beri-beri.

Aneurine plays a part in maintaining normal growth in children; and there is increased need for it during pregnancy and lactation, as well as when the metabolic rate is high. When its deficiency is responsible for lack of appetite or other symptoms described above, its administration is rapidly curative. It is prophylactic and curative in beri-beri, although the nervous symptoms may persist for months. Mild cases can be treated by oral dosage with the Tablet; but, in severe cases, subcutaneous or intramuscular injections of Aneurine Hydrochloride are rapidly beneficial, and one injection produces effects lasting for many weeks. **Marmite**, a yeast extract, and **Bemax**, from cereal embryos, are concentrates of Vitamin B.

Aneurine is sometimes useful in various neuroses, such as toxic neuritis from diphtheria and chronic alcoholism, which latter may impair its absorption. It has also been given for atonic constipation with unreliable results.

Riboflavina.—Riboflavine. Lactoflavin. Vitamin B_2. 6 : 7-dimethyl-9-(d-1′-ribityl)-*iso*alloxazine. Obtained from yeast, other natural sources and by synthesis. A water-soluble factor.

CHARACTERS.—An orange-yellow crystalline powder, slightly soluble in water, taste bitter; more soluble in physiological saline, 10% urea solution and in dilute aqueous alkali hydroxide solutions. Solutions, especially if alkaline, deteriorate if exposed to light.

Dose.—*Prophylactic (daily):*
Metric, 1 to 4 mg; Imperial, 1/60 to 1/16 gr.
Therapeutic (daily):
Metric, 5 to 10 mg; Imperial, 1/12 to 1/6 gr.

ACTIONS AND USES

Riboflavine, a tissue oxidation factor, is found as a pigment in yeast, milk, cheese and eggs. When it is phosphorylated and conjugated with proteins, e.g. adenine, nucleic acid and flavoproteins, it forms a "respiratory enzyme" which is responsible for the oxidation of carbohydrates, aldehydes, lactic acid and amino acids. A deficiency of it in man is uncommon.

Riboflavine is absorbed from the alimentary tract, is stored mainly in the liver, and any surplus in the body is excreted by the kidney as uroflavine. The daily requirement is 2 or 3 mg, but doses of 40 mg may be given and are advised in patients suffering from diarrhœa which impairs absorption. Ariboflavinosis gives rise to combined oral, skin and ocular lesions. Linear fissures (cheilosis) appear at both angles of the lips, which are shiny and red; the tongue becomes fissured and magenta-red, and its papillæ are flattened. A scaly seborrhœic or greasy desquamation with crusts may form at the edges of the lips, nostrils, eyelids and upon the ears. Photophobia, visual impairment in dim light, lachrymation and a sensation of itching or burning in the eyes, associated with bilateral dilatation of the sclerotic vessels and capillary invasion of the cornea (circum-corneal injection or vascularization) precede the development of keratitis.

Administration of Riboflavine relieves this complex of deficiency symptoms within two or three days, but such symptoms individually are not necessarily due to Riboflavine deficiency. Riboflavine is on trial in the treatment of similar skin and ocular disorders.

Pyridoxine Hydrochloride (B.P.C.).—Adermin. Vitamin B_6. 2-methyl-3-hydroxy-4: 5-di-(hydroxymethyl)-pyridine. $C_5H.CH_3.OH.(CH_2OH)_2$.

CHARACTERS.—A white, crystalline powder.

Dose (*not official*).—Orally, **20 to 100 mg (1/3 to 1½ gr.)**.

ACTIONS AND USES

Pyridoxine is available in cereals, yeast and liver. It is concerned with other enzymes in the metabolism of amino acids, and may have an influence on blood formation; its deficiency in dogs causes anæmia and degenerative nerve changes, and, in rats, dermatitis. Its deficiency in man has not been established. It has been given for amyotrophic lateral sclerosis, muscular dystrophy, paralysis agitans, granulocytopenia, and X-ray sickness both orally and intravenously, but without producing material or uniform benefit.

Acidum Nicotinicum.—Nicotinic Acid. Niacin. Pyridine-3-carboxylic acid. Pellagra-preventing (P.P.) Factor. $C_5H_4N.COOH$. Obtained by oxidizing nicotine.

CHARACTERS.—White or cream crystals, taste feebly acid. *Solubility.*—1 in 75 of water.

Dose.—*Prophylactic* (*daily*):

Metric, 15 to 30 mg; Imperial, 1/4 to 1/2 gr.

Therapeutic (*daily*):

Metric 50 to 250 mg; Imperial, 3/4 to 4 gr.

Preparation

Tabellæ Acidi Nicotinici.—50 mg (3/4 gr.) in each.

Nicotinamidum.—Nicotinamide. Pyridine-3-carboxylic acid amide.

CHARACTERS.—White crystalline powder, taste bitter. *Solubility.*—1 in 1 of water.

Dose.—*Prophylactic* (*daily*):

Metric, 15 to 30 mg; Imperial, 1/4 to 1/2 gr.

Therapeutic (*daily*):

Metric, 50 to 250 mg; Imperial 3/4 to 4 gr.

Preparation

Tabellæ Nicotinamidi.—50 mg (3/4 gr.) in each.

ACTIONS AND USES

In the body, Nicotinamide is a component of co-enzymes I and II which are co-dehydrogenases concerned with the conveyance of hydrogen in oxidation-reduction reactions in the tissues. Because Nicotinic Acid lowers the blood-sugar level, it has been given in diabetes mellitus to augment the action of Insulin.

Nicotinic Acid commonly produces a tingling or burning sensation and **vaso-dilatation** in the face, neck, arms and hands, rarely in the feet, together with some feeling of faintness, although the blood-pressure is not much altered; the effect usually lasts about an hour. Small repeated doses have been used with benefit in migraine and for finger chilblains; but they are of no value in hyperpiesia, although prolonged relief from angina pectoris has been claimed. The vaso-dilator action is not possessed by Nicotinamide. Nicotinic Acid is no longer regarded as a prophylactic against porphyrinuria, or as a specific for Vincent's infection.

Deficiency of Nicotinic Acid or its amide is one factor in causing **pellagra**. Nicotinamide is now usually given in treatment in order to avoid itching and flushing of the lesions. Within a few days, Nicotinamide improves the symptoms of erythematous dermatitis, stomatitis and inflammations of other mucous membranes, diarrhœa and early nervous conditions; in three weeks' treatment, cure may be effected. In cases where polyneuritis, cheilosis or other symptoms persist, Aneurine or Riboflavine should be given as pellagrins are usually deficient in more than one B-factor, and the diet should be rectified.

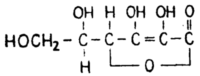
Folic Acid, Vitamin B_c *or M, is discussed on p.* 214*; Vitamin* B_{12} *on p.* 215.

VITAMIN C. The Antiscorbutic Factor (Water Soluble).

Acidum Ascorbicum.—Ascorbic Acid, Vitamin C. Cevitamic acid. The enolic form of 3-keto-1-gulofuranolactone. O.CO.C(OH): C(OH). CH.CHOH.CH$_2$OH.

SOURCE.—It may be obtained from the ripe fruit of Capsicum annum and other vegetable sources, or by synthesis. It is present richly in lemons, oranges, tomatoes, currants and rose hips.

CHARACTERS.—Minute colourless crystals with citrous taste, readily soluble in water and unstable to heating in air or oxygen. Solutions, if neutral or alkaline, oxidize rapidly.



Vitamin C

Dose.—*Prophylactic (daily):*

Metric, 25 to 75 mg; Imperial, 2/5 to 1¼ gr.

Therapeutic (daily):
Metric, 0·2 to 0·5 G; Imperial, 3 to 8 gr.

Preparation

Tabellæ Acidi Ascorbici.—50 mg (3/4 gr.) in each.

ACTIONS AND USES

The adrenal cortex, liver and other tissues store reserves of Ascorbic Acid, excess of which is excreted in the urine at an average rate of 30–35 mg daily. Deficiency of Ascorbic Acid for about two months is required to exhaust the body's reserves.

The chief function of Ascorbic Acid is the formation and **maintenance of the intercellular cement substance**, or **collagen,** which is important for the strength or withstanding of strains in fibrous and osseous tissues, and in the lining of the capillaries; it does not modify the mesodermal connective-tissues cells or their proliferation. From its deficiency, the capillary walls will show increased permeability and fragility, and will rupture easily; cartilage, bone, periosteum, and dentine become structurally imperfect; and there is a delayed healing or adhesion of the mesodermal connective tissues of wounds. Ascorbic Acid is also involved in febrile metabolism when the urinary output falls considerably, but there is no evidence of any protective effect from it.

Prolonged deficiency of Ascorbic Acid results in **scurvy,** exhibited (*a*) in adults by swollen, spongy, bleeding gums and loose teeth; petechial hæmorrhages, ecchymoses, or ulcers on the skin of the legs; and œdematous swellings around the joints. (*b*) in infants, by capillary fragility; acute tenderness of the legs and swellings, due to subperiosteal hæmorrhages, on the tibia or femur at the knee-joints. A diet of condensed milk may be a cause in infants.

Ascorbic Acid is prophylactic and curative for infantile and adult scurvy. Oral dosage suffices to produce improvement rapidly and the urinary excretion serves as a criterion of saturation. It may be given as orange or lemon juice, rose-hip syrup, or as the Tablets of the Acid.

Ascorbic Acid has also been found valuable in treating capillary fragility in children and in accelerating the healing by fibrous tissue in wounds and fractures. It is advisable to give it during febrile illnesses, particularly if chronic, both to replace the reserves and to serve as a thirst-quenching drink, e.g. as fruit juice. Large doses are harmless but act as saline diuretics.

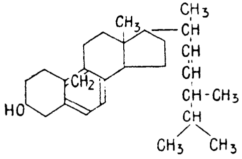
VITAMIN P.

A mixture of two flavone glycosides, Hesperidin and Eriodictyol; it occurs in association with Vitamin C and was thought to decrease capillary permeability but has not proved effective.

VITAMIN D. The Antirachitic Factor (Fat Soluble).

Calciferol.—Calciferol. Vitamin D_2.

SOURCE.—Prepared by the ultra-violet irradiation of Ergosterol in a suitable solvent (e.g. Arachis Oil). 1 mg contains 40,000 Units of Anti-rachitic Activity (Vitamin D). Vitamin D is richly present in Cod-liver Oil, milk, cream, butter, and egg yolk. The natural Vitamin D_3 is irradiated 7-dehydro-cholesterol.



Calciferol

CHARACTERS.—White, needle-like crystals, insoluble in water, soluble in alcohol and in 50 to 100 parts of vegetable oils.

Doses.—*Prophylactic* (*daily*), *infants and adults*. 1,000 *to* 4,000 *Units:*
Metric, 0·025 to 0·1 mg; Imperial, 1/2400 to 1/600 gr.
Therapeutic (*daily*). 2,000 *to* 20,000 *Units:*
Metric, 0·05 to 0·5 mg; Imperial, 1/1200 to 1/120 gr.

Preparations

1. Liquor Calciferolis.—A solution of Calciferol in a suitable vegetable oil (e.g. Arachis). 1 G contains 3,000 Units of antirachitic activity (Vitamin D).

CHARACTERS.—A pale-yellow, oily liquid, taste bland.

Doses.—*Prophylactic* (*daily*), *for infants and adults*. 1,000 *to* 4,000 *Units:*
Metric, 0·3 to 1·2 Mils; Imperial, 5 to 20 min.
Therapeutic (*daily*). 2,000 *to* 20,000 *Units:*
Metric, 0·6 to 6 Mil; Imperial, 10 to 100 min.

2. Liquor Vitamini D Concentratus.—Concentrated Solution of Vitamin D. A suitable or blended fish-liver oil, or a source of Vitamin D, e.g. Calciferol, in a suitable vegetable oil, e.g. Arachis. 1 G contains 10,000 Units of antirachitic activity (Vitamin D) and *not more* than 5,000 Units of Vitamin A (Standardized).

CHARACTERS.—A yellow, oily liquid.

Dose.—*Prophylactic* (*daily*). 1,000 *to* 4,000 *Units.*
Metric, 0·1 to 0·4 Mil; Imperial, 1 to 10 min.

Therapeutic (*daily*). 2,000 *to* 20,000 *Units.*
Metric 0·2 to 2 Mils; Imperial, 3 to 30 min.

3. **Liquor Vitaminorum A et D Concentratus.**—Concentrated Solution of Vitamins A and D. A suitable or blended fish-liver oil or sources of Vitamins A and D in a suitable vegetable oil, e.g. Arachis. 1 G contains 50,000 Units of Vitamin A activity and 5,000 Units of antirachitic activity (Vitamin D) (Standardized).
CHARACTERS.—A yellow, oily liquid, taste bland or fishy.
Dose.— *Daily. Vitamin A*, 2,500 *to* 25,000*: Vitamin D*, 250 *to* 2,500 *Units.*
Metric, 0·06 to 0·6 Mil; Imperial, 1 to 10 min.

Oleum Morrhuæ.—Cod-liver Oil. The fixed oil extracted from the fresh liver of the cod, Gadus morrhua, and other species, and freed from solid fat by filtration at about 0° C.

CHARACTERS.—Pale yellow, odour slight, not rancid; taste bland, fish-like.

COMPOSITION.—Cod-liver Oil, which is rich in *Vitamins A and D* consists chiefly of *unsaturated fatty glycerides*, mainly of docosahexenoic acid, $C_{22}H_{32}O_2$, and an unsaturated acid; and *cholesterol.*

STANDARDS.—Oleum Morrhuæ is standardized for Vitamin A activity (*see* p. 188); and for Vitamin D (antirachitic activity) in comparison with a Standard Preparation, upon litters of recently weaned rats kept on a rachitogenic diet (*a*) *curative*: by its healing effect, as shown by X-ray photographs of the epiphyses of the leg bones taken before and 14 days after treatment, or by comparison of the stained bones with a standard scale; and (*b*) *prophylactic*: by determining the average percentage weight of ash after 4 or 5 weeks' treatment in the femora or humeri of the rats.

Dose.—*Daily in divided doses:*
Metric, 4 to 12 Mils; Imperial, 60 to 180 min.

Preparations

1. **Emulsio Olei Morrhuæ.**—Cod-liver Oil 50 per cent. emulsified with Acacia and Tragacanth and flavoured with Volatile Oil of Bitter Almond, Saccharin and Chloroform.
Dose.—*Daily in divided doses:*
Metric, 8 to 24 Mils; Imperial, 120 to 360 min.

2. **Extractum Malti cum Oleo Morrhuæ.**—Cod-liver Oil 15 per cent. (v/v) in Extract of Malt.
Dose.—*Daily in divided doses:*
Metric, 4 to 30 Mils; Imperial, 60 min. to 1 fl. oz.

Symptoms of Deficiency.—Deprivation of Vitamin D produces **rickets** and **defective calcification of the teeth**. Rickets may arise whatever be the relative or absolute intake of calcium and phosphorus if Vitamin D be absent from the diet, but in its presence a maximum of calcium and phosphorus absorption and utilization is ensured. Its main actions are to lessen the formation of unabsorbable calcium soaps by reducing the intestinal alkalinity;

and probably to assist phosphatase in depositing calcium phosphate in bones.

In rickety children the bones, being less rigid, become bent in supporting the weight, and the defective calcification of the epiphyses is shown by radiographs.

The harmful effect of lack of Vitamin D on the growth of teeth and their resistance to caries was found by experimental work on dogs, and proved by the direct relationship between the healthy state of children's teeth and the richness of their usual diet in Vitamin D. When Vitamin D has been deficient in the diet, the teeth, on eruption, exhibit malformations together with superficial irregularities and a pitted appearance; sections reveal that the enamel and dentine are about one-third their normal thickness and are imperfectly calcified, while the dentinal tubules are irregularly formed and show interglobular spaces. Teeth of this type in children were found to be commonly carious and it was proved that not only was Vitamin D prophylactic against the eruption of malformed or imperfectly calcified teeth but that it could also arrest the spread of caries by stimulating the production around the lesion of a well-formed and well-calcified secondary dentine; but it cannot cure caries. Cereals, particularly oatmeal, which contain unabsorbable inositol phosphate, if they form a high proportion of the diet, have a deleterious influence on the calcification of teeth, but Vitamin D counteracts this effect.

Excessive Administration.—Prolonged large doses of Vitamin D cause a great increase in the calcium content of the plasma and the deposition of calcium in the blood-vessels (e.g. aorta, coronaries, etc.), kidneys and lungs; calculi may form in the bladder. There is no reason to fear such effects from ordinary doses.

USES

Calciferol, Liquor Calciferolis, or Vitamin D, and foods such as Cod-liver Oil, containing Vitamin D, are prophylactic and **curative for rickets**; they are advisable for children living in smoky or sunless surroundings and for patients whose diet cannot be amended to contain an adequate amount of Vitamin D. The antirachitic principle in fish oils and other natural sources, namely dehydrocholesterol or D_3, is more efficacious in treatment than Calciferol (D_2). Calciferol, orally in doses of 50,000 to 150,000 Units daily, if tolerated, slowly improves and possibly cures **lupus vulgaris** after an initial stage of exacerbation in the lesions; treatment for six months or more is necessary.

To ensure efficient calcification of infantile teeth, it is important that the mother should receive pre-natally and during lactation adequate supplies of this Vitamin which she may pass on to the infant. Exposure to sunlight and the use of suitable foods during childhood may do much to diminish the incidence of dental caries in permanent teeth.

Osteo-malacia, which affects women particularly during or after pregnancy, is also cured by Vitamin D with Calcium, and is obviously due to the drain by the child on the mother during pregnancy and lactation. Calciferol, by raising the blood calcium, improves infantile tetany, and large doses (15 to 20 mg.) have proved useful in the hypocalcæmia from lack of parathyroid secretion.

Cod-liver Oil is absorbed slowly if rubbed into the skin and has been employed thus as a nutrient for marasmic babies.

Internally.—Cod-liver Oil is one of the most easily digested and assimilated of fats. The unsaturated fatty acids which it contains aid the assimilation of other fats and, after absorption, they decrease nitrogen metabolism. Cod-liver Oil is, therefore, a very **valuable food** and is prescribed largely as a nutrient in debility, in convalescence and in chronic diseases associated with malnutrition. It is made palatable by giving it in flavoured emulsion, or as the Extract of Malt with Cod-liver Oil, which is acceptable by children.

There is no evidence that the unsaturated fatty acids enter the fatty envelope of the tubercle bacillus or inhibit its growth, but Cod-liver Oil is used as a nutrient in pulmonary and other types of tuberculosis.

Because Cod-liver Oil is unusually rich in Vitamins A and D, it is given when these accessory food factors are deficient in the diet; the Vitamin A promotes growth in the young and maintains healthy epithelial tissues, while Vitamin D ensures good calcification of bones and teeth.

Extractum Malti.—Malt Extract. Prepared from malted barley, Hordeum distichon, or a mixture with not more than 33% of malted wheat, by digestion with water, straining and evaporating under reduced pressure below 55° C.

CHARACTERS.—A yellowish-brown, viscous liquid; odour pleasant; taste sweet. Contains nitrogen equivalent to 4% of protein.

COMPOSITION.—Malt Extract consists chiefly of *maltose*, *dextrin; albumins*, including an active ferment *diastase*; and the soluble phosphates of the barley.

Dose.—*Daily in divided doses:*

Metric, 4 to 30 Mils; Imperial, 60 min. to 1 fl. oz.

Preparation

Extractum Malti cum Oleo Morrhuæ.—Contains 15% (v/v) Cod-liver Oil.
Dose.—*Daily in divided doses:*
Metric, 4 to 30 Mils; Imperial, 60 min. to 1 fl. oz.

ACTIONS AND USES

Malt Extract is **nutritive**. Diastase, of which the amount varies, has little value in therapeutics. Maltose does not readily give rise to acidity and dyspepsia and the Extract is a valuable food in wasting diseases. Malt Extract is a very good vehicle for various insoluble or nauseous drugs, such as Cod-liver Oil.

VITAMIN E. An Antisterility Factor (Fat Soluble).

SOURCE.—It is present richly in the oils from the germs of cereals, in lettuces and peas.
COMPOSITION.—An alcohol, $C_{29}H_{50}O_2$, named *α-tocopherol.*

Tocopherylis Acetas (B.P.C.).

Dose.—Metric, 3 to 10 mg; Imperial, 1/20 to 1/6 gr.

Symptoms of Deficiency.—Lack of this Vitamin causes in rodents, but not in man, irreversible degenerative changes in the testicular germinal epithelium, and in female animals—although the ovaries are not influenced and impregnation is still possible—intra-uterine death of the fœtus with subsequent resorption, or abortion.

USES

Tocopherol or Wheat Germ Oil, 5 Mils (75 mins.) daily is of no value to avert or treat habitual and threatened abortion, or to treat sterility, muscular dystrophies or tabes dorsalis.

VITAMIN K. The Coagulation or Prothrombin Vitamin (Fat Soluble).

SOURCE.—Vitamin K is contained in liver fat and other tissues, green vegetables, cereals, and is formed in the intestine by E. coli. The natural vitamin is 2-methyl-3-phytyl-1: 4-naphthaquinone.

Menaphthonum.—Menaphthone. Menadione. Kapilon. Synkairt. 2-methyl-1: 4-naphtha-quinone. $C_4H_4.C: C.CO.CO.CH.C(CH_3)$.

CHARACTERS.—A yellow, crystalline powder, odour faint; decomposes in sunlight, becoming brown; irritant to skin and mucosæ. *Solubility.*—Insoluble in water, soluble 1 in 50 of fixed oils.
Dose.—*Daily, by intramuscular injection:*
Metric, 1 to 5 mg.; Imperial, 1/60 to 1/12 gr.

Preparation

Injectio Menaphthoni.—A sterile solution in Ethyl Oleate or a suitable oil 5 mg. (1/12 gr.) in 1 Mil (15 min.).

Acetomenaphthonum.—Acetomenaphthone. 1 : 4-diacetoxyl-2-methyl-naphthalene. $C_4H_4.C: C.C(O.CO.CH_3): CH.C(CH_3): C(O.CO.CH_3)$.

CHARACTERS.—A white, crystalline powder with slight acetous odour; almost insoluble in water.

Dose.**—Orally: **Metric, 2 to 10 mg; Imperial, 1/30 to 1/6 gr.

Preparation

Tabellæ Acetomenaphthoni.—*5* mg (1/12 gr.) *in* each.

ACTIONS AND USES

Vitamin K and other naphthaquinones **stimulate the production of prothrombin** by the liver; deficiency of Vitamin K will, therefore, retard the coagulation of blood and predispose the patient to hæmorrhages. Menaphthone and Acetomenaphthone are rapidly effective and can raise the prothrombin content of the blood to normal within 24 to 48 hours.

Deficiency of prothrombin in the blood occurs in infants during the first week of life before bacterial synthesis in the intestine is established; in adults with obstructive jaundice owing to the absence of bile to aid absorption of the fat-soluble naphthaquinone; and in cases of sprue, cœliac disease and persistent diarrhœa owing to lack of absorption of the Vitamin.

Menaphthone by intramuscular injection is used in urgent cases, but Acetomenaphthone, given orally, is soon absorbed. It must be realized that they are of no value unless the hæmorrhagic condition is due to deficiency of prothrombin. They are used in the hæmorrhagic diseases of the new-born, e.g. icterus and melæna neonatorum, both for treatment and for prophylaxis when Acetomenaphthone is given to the mother for a week before labour, or Menaphthone by injection at the commencement of labour. When the maternal prothrombin level is low, they are given to avoid post-partum hæmorrhage.

For a week prior to and following operations on the biliary tract, Acetomenaphthone is given to obviate severe hæmorrhage or, if operation is urgent, Injection of Menaphthone acts more quickly. When Dicoumarol has been given in overdose, Injection of Menaphthone is used to restore the prothrombin level and shorten the coagulation time.

Methionine.—$CH_3.S.CH_2.CH_2.CH(NH_2).COOH$.

CHARACTERS.—A white, crystalline powder.

Dose.—*Orally:* **1 to 2 G (15 to 30 gr.) daily.**

ACTIONS AND USES

Methionine is a sulphhydryl-containing amino-acid, which decreases the fat content of the liver and protects the liver from the toxic action of Chloroform, Carbon Tetrachloride, Organic Arsenicals, or other liver poisons, and from liver cirrhosis. Methionine acts as a methyl donor for the synthesis of choline which *decreases the liver fat by forming phosphatides.*

The effect can be achieved by giving in water, by mouth, Casein Hydrolysates, which are rich in Methionine, but they are usually unpleasant. Methionine may be given orally suspended by Tragacanth in water, or, in urgent cases, by intravenous drip of a solution of Methionine 1 per cent., with Dextrose 5 per cent. in Water for Injection. A high protein diet and Cysteine have similar effects; conversely, a low protein diet predisposes to liver damage. Methionine is said to restore normal blood-clot retraction in purpura hæmorrhagica.

Casein Hydrolysate.—A buff-coloured powder, consisting of about 60% of amino-acids with polypeptides and other products.

ACTIONS AND USES

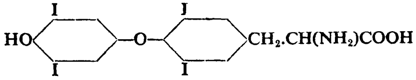
It is given orally suspended in water to replace protein loss or when protein absorption is defective. Forms free from pyrogens may be given by intravenous drip in aqueous solutions containing 5 to 10 per cent. Dextrose and from 2·5 to 10 per cent. amino-acids.

DRUGS INFLUENCING METABOLISM—HORMONES

The drugs which regulate the metabolic processes of the body are the hormones or internal secretions of the endocrine glands —thyroid, parathyroid, pancreas, suprarenal, pituitary, liver and others.

Thyroideum.—Thyroid. Dry Thyroid. Prepared from thyroid glands of oxen, sheep or pigs by removing the connective tissue and fat, drying them below 60° C., powdering and extracting all fat with light petroleum and drying the residue.

COMPOSITION.—It contains 0·1% of Iodine in combination as *Thyroxine*, which is racemic diiodo (diiodo-hydroxyphenoxy) phenyl amino-propionic acid.



CHARACTERS.—A cream-coloured, amorphous powder; odour and taste faint, like meat.

Dose.—Metric, 30 to 120 mg; Imperial, 1/2 to 2 gr.

Preparation

Tabellæ Thyroidei.—30 mg (1/2 gr.) in each.

ACTIONS AND USES

Thyroxine, the internal secretion of the thyroid, **accelerates the basal metabolic rate**; deficiency of it produces cretinism in infants and myxœdema in adults. The secretion of Thyroxine is controlled by the thyrotrophic hormone of the anterior pituitary. The body contains about 12–14 mg of Thyroxine, which is destroyed at the rate of 0·2–0·4 mg per day; therefore this amount, corresponding to 60 and 120 mg (1 to 2 gr.) Thyroid, may be necessary to maintain the basal metabolic rate in myxœdema or after removal of the thyroid.

Thyroid is given orally, in tablets, one hour before meals, commencing with doses of 20 mg (1/3 gr.), less in children, once or twice daily, and increased gradually.

The metabolic effects of Thyroid, given by mouth, do not commence until about a day after administration, reach a maximum only after 6–10 days, and take 3 or 4 weeks to subside to normal; Thyroid is therefore **cumulative** and dosage by mouth must be increased with care.

Administration of Thyroid produces (1) increased consumption of oxygen and output of carbon dioxide; (2) augmented protein metabolism with increased excretion of urea and total nitrogen; (3) profuse diuresis, partly due to the increased urea; (4) increased oxidation of the fats and carbohydrates of the body. Of the consequent loss in weight about a sixth is due to protein and five-sixths to fat and carbohydrate katabolism. The augmented carbohydrate katabolism is due to mobilization of the hepatic glycogen, and the sugar so released, if not dealt with by Insulin, will cause glycosuria, which thus serves as a symptom of overdosage. A single dose of 1 Mg Thyroxine, or 0·3 G Thyroid, augments the basal metabolism by 2 per cent. but it should be noted that the effects of repeated small doses are additive and eventually more potent than widely-spaced large doses.

Frequent dosage with Thyroid readily causes "**hyperthyroidism**"—symptoms of nervous, circulatory and metabolic types, namely headache, muscular weakness and pains, fine tremors in the limb muscles, and nervous temperament; the pulse rate increases and palpitation is felt, the skin vessels dilate and sweating results; dilated pupils are commonly present but rarely exophthalmos; and there is a rapid loss in weight. The increased cardiac rate is due to sensitization of the sympathetic endings to Adrenaline.

The *therapeutic value* of Thyroid is in the treatment of (1) **cretinism**, in which condition the child, after weaning, fails to develop mentally or to grow; it remains dwarfish, with thickened, dry skin, a protruding tongue and prominent abdomen. Thyroid is not curative, but continued dosage (1/2 to 1 gr. Thyroid daily) can transform an idiot into a presentable and reasonable being if the condition be treated in time; (2) **myxœdema** in adults, in which the patient shows mental dullness and physical lethargy with sluggish reflexes; the skin is dry, the hair is shed, and the subcutaneous tissues become thickened, hence the face, limbs and hands look œdematous but do not pit on pressure; metabolism is low, temperature below normal; cardiac enlargement, a weak pulse and atheromatous degeneration of vessels occur commonly. Thyroid is curative in myxœdema, but must be continued in regulated dosage during life. In exophthalmic goitre or adenoma of the thyroid, with symptoms of thyrotoxicosis, dosage with Thyroid would obviously be harmful.

Thyroid is effective in **reducing obesity** but it should be used only as an adjuvant to dietetic treatment and in small doses only; additional protein is advisable to repair nitrogenous loss and care is necessary to avoid over-dosage.

Administration of Thyroid has proved of considerable value in various **skin diseases**, such as psoriasis, ichthyosis, chronic eczemas, etc.; no explanation is available of its action other than that of accelerated metabolism.

Thiouracilum.—Thiouracil. 2-mercapto-4-hydroxypyrimidine. $C_4H_2N_2.SH.OH$.

CHARACTERS.—A white or cream powder, taste bitter; slightly soluble in water.

Dose.—Metric, 0·1 to 0·2 G; Imperial, 1½ to 3 gr.

Preparation

Tabellæ Thiouracili.—0·1 G (1/2 gr.) in each.

Methylthiouracilum.—Methylthiouracil. 2-mercapto-4-hydroxy-6-methylprimidine. $C_4HN_2.CH_3.SH.OH$.

CHARACTERS.—A white or cream powder, taste bitter; slightly soluble in water.

Dose.—Metric, 0·1 to 0·2 G; Imperial, 1½ to 3 gr.

Preparation

Tabellæ Methylthiouracili.—0·1 G (1½ gr.) in each.

ACTIONS AND USES

Thiouracil and Methylthiouracil inhibit the cellular synthesis of thyroxine by preventing the combination of iodine with tyrosine to form thyroxine.

Both drugs, given in dose of 0·1 to 0·2 G (1½ to 3 gr.) thrice daily, begin to act after an interval of about ten days, during which the preformed thyroxine is still functioning. They relieve the tremors, nervousness and, in some cases, the exophthalmos of thyrotoxicosis; the thyroid gland may at first become larger and softer (owing to an increase in the thyrotrophic hormone) and then decreases in size; the basal metabolic rate is lowered, hence the weight increases; the heart rate becomes slower and palpitation is relieved.

After three weeks' treatment, the dosage is reduced to 0·2 G (3 gr.) daily and a minimum maintenance dose established by the effect on the pulse rate, weight curve, and metabolism. With Methylthiouracil, a dosage of 25 mg (2/5 gr.) given twice weekly may be adequate for maintenance.

Methylthiouracil, the less toxic, is generally prescribed and it is effective in controlling the symptoms of thyrotoxicosis particularly in primary cases; in a considerable proportion of these, the symptoms do not recur when treatment is discontinued, but others may require maintenance doses under supervision for a long time. Methylthiouracil is safe and usually successful for controlling relapses, but then may be considered as a preparatory measure to operative treatment, before which Lugol's Iodine may be given to decrease the vascularity of the gland.

Briefly, it may be said that in the young, and in elderly persons with cardio-vascular complications, Methylthiouracil is preferable to operation because it is safer and allows a more rapid return to work; but it is less satisfactory for reducing the goitre, and, if this is causing discomfort or pressure symptoms, operation is advisable. With these drugs, thyrotoxic auricular fibrillation usually reverts to a normal rhythm; and successes have been recorded from their use in angina pectoris.

Toxic Effects.—Care is necessary in the use of the Thiouracils which commonly cause urticarial skin rashes, nausea, drug fever and glandular enlargement. More serious are their later effects in decreasing the numbers of granulocytes and leucocytes; therefore, to obviate agranulocytosis and leucopenia, regular leucocyte counts are desirable during treatment. Methylthiouracil is less liable to cause these toxic reactions.

Propylthiouracil.—*Dose.*—50 mg (3/4 gr.) thrice daily initially, and reduced later to a maintenance dose of 50 to 25 mg daily. Propylthiouracil is more potent than Methylthiouracil but does not act more quickly. It is effective in primary and secondary thyrotoxic cases but is not regarded as superior to Methylthiouracil.

PARATHYROID GLAND EXTRACT (*not official*)

Parathyroideum.—A light-yellow powder.

Dose.—Metric, 3 to 6 mg; Imperial, 1/20 to 1/10 gr. in tablets.

Extractum Parathyroidei.—Parathormone. An aqueous extract of the fresh gland prepared by means of acid. A Unit is 1/100 of the amount required to raise the plasma calcium of a dog (20 Kg) by 5 mg per cent. in 15 hours.

Dose.—10–25 Units by hypodermic injection on alternate days or daily.

ACTIONS AND USES

The secretion of the four parathyroid glands **controls the calcium metabolism** of the body. If the secretion be deficient, the plasma calcium falls from the normal 10 mg per cent. to as low as 5 mg and this causes increased neuromuscular excitability or tetany, which is exhibited by spasms or tremors of the muscles of the face, limbs or hands. Parathyroid extract, given by injection, increases the plasma calcium and thus relieves the condition, but, unless a liberal calcium intake is provided, the increased plasma calcium is derived from the bones. Excessive formation of parathyroid hormone gives rise to an increased excretion of calcium and to softening of the bones (osteitis fibrosa). The absorption of Parathyroid, when given orally, is unreliable.

The effect of Parathyroid is delayed for 4 hours and lasts 20 hours; the maximum rise in blood calcium occurs from 12–18 hours after an injection, therefore repetition of dosage must be spaced with care.

Parathyroid hormone was used to **relieve tetany** arising after thyroidectomy and to check infantile tetany, but equal effects follow the oral use of Calcium Lactate or Gluconate and Vitamin D.

Insulinum.—Insulin. The anti-diabetic principle in the pancreas. It has been crystallized and is a sulphur compound of a complex amino-acid, containing in its molecule cystine, tyrosine, leucine, arginine, glutamic and other amino-acids.

SOURCE.—Prepared from fresh or frozen pancreas by extraction with 60% alcohol and precipitation by absolute alcohol; the precipitated Insulin is dissolved in water and re-precipitated either (1) by adjusting the reaction to the iso-electric point, or (2) by adding trinitrophenol. Insulin precipitated by method (1) may be collected, dried and powdered; but after method (2) the precipitate is dissolved in alcohol acidified with hydrochloric acid, the solution poured into excess of acetone, and the Insulin thus precipitated is dried and powdered.

Assay of Insulin.—The Standard is 0·0455 mg of an Insulin Hydrochloride kept by the National Institute of Medical Research, and samples must produce the same percentage reduction in the blood-sugar as the Standard when injected into rabbits. It may also be assayed by comparing the doses which cause convulsions in mice within one and a half hours.

Assay of Protamine Zinc Insulin.—It must comply with a test for the biological assay of Insulin, and also a test for the retardation of Insulin effect.

Labelling.—Each Insulin container shall be labelled with the number of Units per Mil, and a label on it, or the wrapper, shall state the date of manufacture and the date after which the preparation is not intended to be used.

Storage: If kept below 20° C., it should retain its potency for at least two years.

Injectio Insulini.—Injection of Insulin. a sterile solution of the specific antidiabetic principle of the mammalian pancreas, containing 20, 40 or 80 Units per Mil.

CHARACTERS.—A colourless, clear liquid contained in sealed glass phials (usually containing 5 or 10 Mils) which allow the withdrawal of successive doses. Unless otherwise ordered, a strength of 20 Units per Mil shall be dispensed.

Dose.—*By injection:* Determined by the physician in accordance with the needs of the patient.

Injectio Insulini Protaminati cum Zinco.—Injection of Protamine Zinc Insulin. A sterile solution of the specific antidiabetic principle of the mammalian pancreas with a suitable protamine and zinc chloride, containing 40 or 80 Units per Mil.

CHARACTERS.—An almost colourless, turbid liquid, contained in sealed glass phials (5 or 10 Mils) which allow of withdrawal of successive doses. Unless otherwise ordered, a strength of 40 Units per Mil shall be dispensed.

Dose.—*By injection:* Determined by the physician in accordance with the needs of the patient.

ACTIONS AND USES

Insulin, the hormone formed by the β-cells in the Islets of Langerhans, lowers the percentage of blood-sugar in proportion to the number of Units injected. Oral administration is useless because Insulin is destroyed by pepsin and trypsin; only small and unreliable amounts are absorbed from the rectum, skin, or from below the tongue. Insulin is best **given by hypodermic injection**, except in urgent cases, when intravenous injection is necessary; intramuscular injections may cause local necrosis.

The maximal reduction in the blood-sugar occurs about 2–4 hours after the injection and, depending upon the dose and the intake of carbohydrates, the percentage of blood-sugar rises again gradually to gain its former level in about 6–8 hours; repeated dosage with Insulin is therefore necessary, and it should be given about half an hour before meals so that its maximal effect may coincide with the maximal absorption of carbohydrates.

Pharmacological Action.—**Insulin increases the capacity of the tissues to metabolize sugar and** the capability of the liver and muscles **to store glycogen.** In an eviscerated mammal, Insulin will lower the blood-sugar, but only 25 per cent. of the reduction is due to accelerated metabolism as determined by the increased oxygen consumption and carbon dioxide output; the remaining 75 per cent. has, therefore, been stored as glycogen by the muscles. In the intact animal, (1) it causes increased metabolism of sugar in the muscles, with consequent rise in the respiratory quotient; (2) it also increases the storage of glycogen in both the liver and muscles; and (3), it inhibits the power of the liver to produce sugar from proteins. Insulin is excreted in the urine unchanged; a single dose is completely excreted within 24 hours.

Toxic Effects. **Hypoglycæmia.**—In rabbits, a dose capable of lowering the blood-sugar to 45 mg per cent. or less produces increased reflex excitability, rapid shallow respiration, strychnine-like convulsions, coma and death. **In man**, when the blood-sugar level falls from 100 to 70 mg per cent. symptoms of hunger, weakness, fatigue, tremulous or inco-ordinate movements, anxiety and nervousness appear, associated with flushing, less often with pallor, and profuse sweating. If the fall be below 50 mg per cent., there is acute mental distress or delirium, followed by convulsions, loss of reflexes, and coma. Such symptoms may also occur when a hyperglycæmia is too rapidly reduced.

The induction of hypoglycaemic convulsions by gradually increasing doses of Insulin is used in the shock treatment of schizophrenia.

The symptoms of **hypoglycæmia can be relieved** if the patient at their commencement takes a lump of sugar, or 5 to 10 G of Medicinal Glucose (Dextrosum Hydratum), because they usually take fifteen minutes to develop severely. If hypoglycæmic coma with inability to swallow has occurred, it can be relieved promptly by Injection of Adrenaline (0·5 to 1 Mil), which mobilizes the liver glycogen or, if there is no glycogen reserve, by Injectio Pituitarii Posterioris (5 Units) which antagonizes the action of

Insulin in the tissues. The injection intravenously of 200 to 400 Mils of 5 or 10 per cent. Dextrose in Normal Saline may be necessary; rectal absorption of Dextrose is too slow for this method to be satisfactory

Diet and Insulin in Diabetes Mellitus.—Although of great value in treating diabetes, Insulin in neither curative nor necessary in all cases. If a diabetic patient can maintain his activities.and weight upon a restricted carbohydrate diet without excreting sugar, Insulin is unnecessary; but, if he cannot, appropriate dosage with **Insulin will enable additional carbohydrate to be utilized.**

In regulating the **diet of diabetics,** it must be remembered that for the complete metabolism of fats and proteins, carbohydrates are essential; if they are deficient, fats are incompletely burned, and β-hydroxybutyric and aceto-acetic acids accumulate in the blood to cause ketosis (acidosis) and the excretion of acetone in the urine and breath; imperfect protein katabolism also results in the production of ketone bodies from certain amino-acids, e.g. leucine and tyrosin. Accumulation of aceto-acetic acid causes diabetic coma, therefore in reducing the carbohydrates in a diabetic dietary, the fat must not exceed the sum of twice the carbohydrates and half the protein; and, since the body requires 1 G protein per Kg, the minimum "antiketogenic" basis per Kg is 1 G carbohydrate (= 4 calories), 1 G protein (= 4 calories) and 2·5 G fat (1 G = 9 calories). Tables of the composition of foods enable a diet to be constructed on these lines to yield an adequate number of calories (for average weights about 2,000) to maintain nutrition. If, on such a diet, the urine remains free from sugar, Insulin is unnecessary.

If, however, on this basal maintenance diet the blood-sugar still remains high and sugar is still excreted in the urine, the daily excretion should be estimated. Now, since **1 Unit of Insulin ensures the metabolism of 2 G of sugar**, the daily Units of Insulin should be one-half the daily excretion of sugar in grammes. The daily dose should be given in two equal amounts, each half an hour before the two principal meals of the day.

A simpler method is to put the patient on a diet containing 50 to 100 G carbohydrate with appropriate protein and fat. If sugar persists in the urine, 5 Units of Insulin are given hypodermically before the two principal meals for three days; if the sugar be still present the dose is increased to 10 Units and then adjusted to the dosage which keeps the urine free from sugar.

Surgical operations on diabetics should be performed only if the blood-sugar has been lowered to normal, or, if urgent, after giving 25 Units of Insulin and 50 G of Dextrose two hours before operation. Any infectious disease, catarrh or influenza invariably lowers the sugar tolerance of diabetics and demands increased dosage with Insulin.

Patients undergoing Insulin treatment should carry supplies of lump sugar or Dextrosum Hydratum which they may take if they feel any symptom of hypoglycæmia. The injection of Insulin, e.g. subcutaneously in the thighs or abdomen, can easily be carried out by patients themselves if they are taught aseptic technique; the sites must be changed as local atrophy of fatty tissue occurs.

Insulin in Diabetic Coma.—Diabetic Coma is due to ketosis or accumulation of the poisonous aceto-acetic acid. Treatment consists in giving Dextrose (50 G) by mouth, if possible, or 20 to 40 G in 10 per cent. solution intravenously, as well as 50 Units of Insulin initially, and 25 Units with additional 25 G doses of Dextrose every 2 or 3 hours until the condition is relieved. The increased metabolism of sugar ensures effective katabolism of the fats and removes the lipæmia, fatty acids and acetone from the blood and tissues. In severe cases, larger doses of Insulin are required and the Dextrose should be given intravenously in more dilute (5 per cent.) solution in Normal Saline as it is important to counteract the dehydration unless plenty of fluid can be taken orally. Injections of 2 per cent. Sodium Bicarbonate in Normal Saline or Ringer-Lactate solution are also used.

Retardation of Insulin's Action.—Insulin in aqueous solution begins to act in half an hour, has its maximal effect in 2 to 4 hours, and the action has subsided in 6 to 8 hours; hence, in young persons it is sometimes difficult to obviate both hypoglycæmia and, at night, hyperglycæmia. Slowly-acting compounds of Insulin have, therefore, come into use.

Globin Insulin with Zinc is a clear solution containing 40 or 80 Units per Mil; it is given subcutaneously. Globin Insulin with Zinc is intermediate in its speed of onset and in duration between Insulin and Protamine Zinc Insulin. It begins to lower the blood-sugar in 2½ to 3 hours; the maximum fall is between the 5th and 8th hour; and the blood-sugar returns to its former level in about 18 hours. Its slower action enables many diabetics to be controlled by one daily injection.

Di-Insulin is a mixture of equal parts of Insulin and phenyl-ureido-insulin (*iso*-Insulin); the latter acts more slowly. Di-Insulin begins to act in an hour, reaches its maximum in three hours and lasts for about eleven hours.

Zinc Protamine Insulin.—This contains per 100 Units about 1 mg of protamine sulphate and 1 mg of zinc, which retard the action. Protamine Zinc Insulin, a fine stable suspension, is also injected hypodermically; it is buffered per 100 Units by 10–11 mg of sodium phosphate and has a *p*H between 6·9 and 7·3.

Zinc Protamine Insulin begins to lower the blood-sugar in 3 to 4 hours after its injection; the maximal action is during the 8th to 12th hour and the action lasts for 24 to 30 hours.

The advantage of these "retarded" preparations is that the fall in the blood-sugar percentage is more gradual and, therefore, the rapid alternations between a high and a low blood-sugar when using ordinary Insulin are obviated. They also permit of wider spacing of the dosage and spreading of the carbohydrate allowance over several meals; but owing to their slower absorption, their action commences too late to control a carbohydrate meal taken soon after their injection.

The respective time defects of soluble Insulin and Zinc Protamine Insulin are overcome by combining the two in appropriate Units in one injection, given usually before breakfast, so that the Insulin deals with the blood-sugar rise from the morning carbohydrate meal, while the Zinc Protamine Insulin maintains the blood-sugar within normal levels during the remainder of the day and night. By careful adjustment of the dietary and repeated estimations of the sugar in the blood and urine, one can arrange that diabetics need only one injection daily.

The slower action of these compounds implies, however, that with the more gradual fall in the blood-sugar, the warning symptoms of hypoglycæmia may be absent and convulsions or coma may develop suddenly; this danger must be guarded against during the night.

Heparinum.—Heparin. A sterile preparation containing the sodium salt of a complex organic acid which delays clotting of shed blood. Heparin is a poly-sulphuric acid ester of mucoitin and is formed in the mast cells which lie mainly along the walls of the small blood-vessels; it is obtained from liver and lung tissue.

CHARACTERS.—A greyish-brown, hygroscopic powder, completely soluble in water. 1 mg contains not less than 75 Units.

Assay.—The Unit is contained in 0·0077 mg of the Standard Preparation; and, in comparison with this, samples of Heparin are assayed on cat's blood run into specific amounts of Heparin, the degrees of clotting being estimated after two hours' incubation at 37° C. Label states number of Units per mg.

Dose.—*By intravenous injection:* **6,000 to 12,000 Units.**

Preparation

Injectio Heparini.—A sterile solution of Heparin in Injection of Sodium Chloride. Labelled with the number of Units per Mil and the date of manufacture; it should not be used later than two years after that date.

Dose.—*By intravenous injection:* **6,000 to 12,000 Units.**

ACTIONS AND USES

Heparin is a rapid but **short-acting anticoagulant**, which (*a*) prevents agglutination and disintegration of the blood platelets, (*b*) prevents the activation of prothrombin into thrombin, and (*c*) inhibits the action of thrombin. In proportion to its dosage, Heparin will delay the coagulation time of the blood from six minutes to about forty minutes; the effect is maximal about thirty minutes after its injection and passes off in one and a half to two hours. Its action is physicochemical due to its electronegative charge; Protamine Sulphate (5 to 10 Mils of a 1 per cent. solution intravenously) is an antidote by neutralising this.

Heparin may be added to drawn blood (1,000 Units per 100 c.c.) when it will delay the coagulation time to forty-five minutes. It may also be injected into a transfusion donor.

Heparin is used in the prevention and treatment of thrombosis which may follow surgical operations or parturition and in facilitating vascular surgery. It will not dissolve clots but will prevent the extension of clotting, hence it is given in thrombophlebitis, and embolism. Owing to its brief action, it would require to be injected every four hours to maintain the effect or be given by continuous intravenous drip; it is commonly used as a preliminary to, or in conjunction with, the use of Dicoumarol.

Dicoumarol.—Dicoumarin. 3 : 3′-methylene-bis-4-hydroxycoumarin.

CHARACTERS.—A white microcrystalline powder; taste slightly bitter. *Solubility*—Slightly in water.

Dose.—*Daily:* **Metric, 50 to 300 mg; Imperial, 3/4 to 5 gr.**

ACTIONS AND USES

Dicoumarol reduces the formation of prothrombin by the liver, and causes an increase in the coagulation time of the blood. Its action take 24 to 48 hours to develop and may then last for from three to seven days; it also increases the plasma prothrombin time.

Dicoumarol, given orally, in dose of 50 to 100 mg (¾ to 1½ gr.)

daily will usually suffice to keep the prothrombin time between 10 and 20 per cent. of the normal; this is the desirable degree of action and, to avoid exceeding it, intermittent dosage is given. The prothrombin or coagulation time should be checked regularly and the prothrombin time should be kept between 30 and 50 seconds.

Dicoumarol is given to maintain the brief anticoagulant effect of Heparin in the prophylaxis and treatment of thrombosis which may be anticipated after gynæcological and other operations, parturition, or in vascular surgery, when it is usual to postpone starting the drug until after three days have elapsed. It is also used to prevent extension of the clot in thrombophlebitis, pulmonary embolism and cerebral embolism. It will not dissolve pre-existing clot.

Dicoumarol must be avoided if further operation may be necessary and, if bleeding occurs during its use, Menaphthone should be given speedily and blood transfusion made available in case of necessity. It should not be used in liver disease.

Extractum Hepatis Liquidum.—Liquid Extract of Liver. A selected fraction of an alcoholic extract of ox or sheep liver, dissolves in a mixture of Glycerin, Alcohol and Distilled Water.

It is prepared by extracting the liver with 80% Alcohol, acidified with sulphuric acid, and then with 50% Alcohol. The filtered extract is evaporated to a syrup and dehydrated by pouring it into Absolute Alcohol; the precipitated extract is dehydrated till brittle, collected on a filter and dissolved in Distilled Water; Glycerin, Alcohol and Distilled Water are added so that 100 Mils contain Extract equivalent to 800 G of fresh liver.

COMPOSITION.—The specific principle which increases the number of erythrocytes in pernicious anæmia. 30 Mils (1 fl. oz.) contain the equivalent of 240 G (8 oz.) of fresh liver.

Dose.—Metric, 30 Mils; Imperial, 1 fl. oz.

ACTIONS AND USES

Liver and its preparations are used to treat hyperchromic macrocytic anæmias, e.g. **pernicious anæmia**, the anæmias of sprue, cœliac disease and dietetic defect. The liver stores a hæmopoietic factor or anti-anæmic principle which is essential for the conversion of the megaloblasts in the bone marrow into normoblasts and reticulocytes. The synthesis of this principle arises from a reaction between a thermolabile "intrinsic factor" secreted in the gastric juice and an "extrinsic factor" present in meats, yeast, and other foods. The product is a thermostable substance which, in purified form, is a buff powder yielding on hydrolysis the amino-acids, arginine, glycine, leucine, hydroxyproline and aspartic acid. In pernicious anæmia an adequate diet of liver causes, within a day or two, a rapid increase in the numbers of reticulocytes, which in eight or ten days may form about 30 per cent. of the total red cells; the reticulocyte count then declines rapidly until after three or four weeks it is again normal. About the third day of treatment there begins a progressive increase in the numbers of erythrocytes and leucocytes and in the hæmoglobin percentage; this continues until a normal blood-picture is re-established and the colour-index returns to normal. Improvement in the clinical symptoms follows, but the achlorhydria, a common symptom, remains unaffected; hence administration of Dilute Hydrochloric Acid with meals is essential in treatment.

Patients may be given 2–4 oz. of lightly cooked liver twice daily but, as this diet becomes tedious, the Liquid Extract of Liver in amounts daily of 30 Mils (1 fl. oz.), corresponding to 1/2 lb. of liver, is preferable along with a diet which is generous in red meat.

Intramuscular injections of Extracts of Liver, concentrated and freed by alcoholic precipitation from proteins so as to avoid allergic reactions, have proved more efficient and economical than oral dosage; thus, an Extract of 10 G Liver, given intramuscularly, has a therapeutic effect equivalent to that of 500 G (1 lb.) Liver, taken by mouth; and by injecting doses of Extracts representing 100 G Liver, it is practicable, owing to the storage of the principle by the liver, to maintain a normal blood picture for about one month. Intramuscular injections also ensure a more rapid therapeutic result and, for urgent cases, specially purified Extracts are available for intravenous administration. In treating a moderate case it is usual to inject amounts of Extract representing 200 to 400 G fresh liver on the first day, then 100 to 200 G daily for 4 days and then a maintenance dosage of 100 G or more monthly.

The following are some of the commonly used Extracts for intramuscular or intravenous use: Anahæmin, Campolon, Examen, Hepastab, Hepatex, Hepol, Parenamps, Pernæmon.

Intramuscular injections may be supplemented by providing lightly cooked liver in the diet or by oral doses of the Liquid Extract of Liver in appropriate amounts daily. Liver therapy is curative in pernicious anæmia but treatment must be maintained throughout life. When subacute combined degeneration of the spinal cord has developed, intramuscular injections produce considerable improvement in the ataxia and knee-jerks. Liver therapy also cures the pernicious anæmia of pregnancy, infantile anæmias, and other macrocytic anæmias, e.g. of sprue and cœliac disease.

Hepar Proteolysatum (B.P.C.).—Proteolysed Liver. A mixture of the products of digestion of mammalian liver by papain.

CHARACTERS.—A greyish-brown powder or paste; odour and taste meaty, not unpleasant.

Dose.—*Daily:* **Metric, 8 to 30 G; Imperial, 1/4 to 1 oz.**

ACTIONS AND USES

Proteolysed liver is more palatable than Liquid Extract of Liver and contains the hæmopoietic factor. It is effective in pernicious anæmia and in the macrocytic anæmias of sprue, pregnancy and malnutrition, especially for cases intolerant of injections of Liver Extracts. Large initial doses are given and maintenance doses are established later.

Acidum Folicum (B.P.C.).—Folic Acid. Pteroylglutamic Acid. Vitamin B_C or M. Lactobacillus casei factor.

CHARACTERS.—An orange-yellow powder, insoluble in cold water. Richly present in liver and yeast, but also available in other foods.

Dose.—*Orally:* **Metric, 10 to 20 mg; Imperial, 1/6 to 1/3 gr.**
Sodium salt, by intramuscular injection:
Metric, 5 to 10 mg; Imperial, 1/12 to 1/6 gr.

ACTIONS AND USES

Folic Acid is essential for the development of megaloblasts to normoblasts. In food, Folic Acid is conjugated with hexaglutamic acid (pteroyl-hexaglutamyl-glutamic acid); in pernicious anæmia, this conjugate cannot be hydrolysed and split; in sprue, it is not absorbed. Folic Acid, orally in doses of 20 to 25 mg (1/3 to 2/5 gr.) daily, or by a single intramuscular injection of 50 to 150 mg (3/4 to 2½ gr.) of the Sodium salt in solution, produces a reticulocyte response and clinical improvement only in macrocytic anæmias with megaloblastic changes in the bone-marrow; but its effects are not so good or so rapid as those of Liver Extract in pernicious anæmia; also it does not improve the subacute combined degeneration. It is also of some value in sprue and other macrocytic megaloblastic anæmias—pregnancy, infantile and pellagra—when the nervous system is not involved. It is usually ineffective in cœliac disease. It should not be regarded as a replacement of Liver therapy.

Vitamin B_{12}.—Anacobin. Cytamen. The hæmopoietic factor isolated from liver, or produced by deep fermentation of Streptomyces griseus. It is available in ampoules containing 20 microgrammes (γ) in 1 Mil.

Dose.—*Intramuscularly:* **10 to 80 microgrammes** (γ).

ACTIONS AND USES

This cobalt-containing anti-anæmic factor is present in minute quantities in liver; it is a red, crystalline substance. It is effective in minute doses for pernicious anæmias and also improves subacute combined degeneration. It causes in the marrow a transformation from megaloblastic to normoblastic formation, and produces a reticulocytosis with a peak on the 5th or 6th day. The rise in the erythrocyte count in 15 days increases with the dosage and is also greater when the initial cell count has been low. The period for complete recovery varies from 15 days to about 4 months. Oral dosage has been found effective but only in amounts 30 to 60 times those required intramuscularly. The recommended dose for pernicious anæmia is 40 to 80 μG initially, 20 μG weekly for 3 months, and 30 μG every 3 weeks afterwards; larger or daily dosage is advised if neurological symptoms are present. Vitamin B_{12} has given good results in pernicious anæmia, nutritional macrocytic anæmias and tropical sprue.

Desiccated Hog's Stomach.—Ventriculin. Gaster Siccata, Gastrexo, etc. Dried preparations of the whole or de-fatted stomach of the hog. 1 G represents about 20 G fresh tissue.

CHARACTERS.—Yellowish powder, almost odourless and tasteless.

Dose.—Metric, 15 to 30 G; Imperial, 1/2 to 1 oz.

ACTIONS AND USES

Hog's stomach contains an "intrinsic factor" which is normally secreted with the gastric juice and reacts with an "extrinsic factor," contained in meats, yeast, etc., to form the anti-anæmic factor, which is stored by the liver and is essential in the bone marrow for the maturation of the megaloblasts into normoblasts and reticulocytes. In pernicious anæmia the "intrinsic factor" is absent. The "intrinsic factor" is destroyed above 70° C., therefore preparations must be given by mouth, suspended in milk or fruit juice, but not in hot fluids. Cases of pernicious anæmia respond as they do to treatment by liver therapy, and about 15 G of dried hog's stomach is equivalent in effect to 300 G of fresh liver. It is of value in cases which are intolerant of, or fail to respond effectively to, liver therapy.

Deoxycortoni Acetas.—Deoxycortone Acetate. D.O.C.A. 21-acetoxy-Δ^4-pregnene-3 : 20-dione.

CHARACTERS.—Colourless crystals or powder; almost insoluble in water, soluble in fixed oils.

Dose.—*By intramuscular injection:*

Metric, 2 to 10 mg; Imperial, 1/30 to 1/6 gr.

Total implantation dose:

Metric, 0·2 to 0·4 G; Imperial, 3 to 6 gr.

Preparation

Injectio Deoxycortoni Acetatis.—A sterile solution for intramuscular injection in Ethyl Oleate or a suitable oil. Contains 5 mg (1/12 gr.) in 1 Mil (15 min.).

ACTIONS AND USES

Deoxycortone Acetate represents the cortical hormone, Corticosterone, of the suprarenal gland. This maintains the balance of the osmotic ions (Na, K, Cl, and PO_4) in the blood and thus regulates the blood-volume.

Addison's Disease is due to deficiency of Corticosterone and this causes excessive excretion of Sodium ions and water, a retention of Potassium ions, a reduction in blood-volume (dehydration) and blood-pressure, and, possibly from impaired carbohydrate metabolism, muscular weakness.

When Deoxycortone Acetate is administered intramuscularly, it begins to act in from a half to one hour; it causes a retention of Sodium ions and greater excretion of Potassium ions, hence, in treating the disease, it may be necessary to restrict the Sodium in the diet and to arrange an additional Potassium intake. A maintenance dose is established for the control of the disease; this is usually less than 10 mg (1/6 gr.) daily.

Subcutaneous implantation of cylindrical pellets (available in 25, 50 and 100 mg doses) obviates frequent injections. The rate of absorption depends on their surface area; from an implant of 50 or 100 mg, the daily absorption respectively is 0·45 or 0·7 mg of Deoxycortone Acetate, and the duration of effect about 100 or 140 days respectively.

Deoxycortone Acetate is not always a complete replacement therapy, and in some cases Extractum Suprarenali Corticis (Cortin), 5 to 10 Mils by injection, aids in the improvement.

Cortisone.—Compound E. An adrenal hormone, having the constitution 17-hydroxy-11-dehydrocorticosterone, prepared synthetically from bile acids.

ACTIONS AND USES

Cortisone has been used with successful results in rheumatoid arthritis. Within a few days, it reduces the pain and stiffness, later the swellings lessen and movements increase, while the blood sedimentation rate and anæmia decrease. It is given intramuscularly in doses of 100 mg; as the disease is a deficiency one, maintenance treatment is necessary to prevent relapses. The pituitary adreno-corticotrophic hormone (ACTH), dose 40 mg daily, produces comparable effects indirectly by stimulating the secretory cells of the adrenal cortex. Other diseases effectively treated are acute rheumatism, infective arthritis, spondylitis and collagen-vascular diseases, lupus erythematosus, periarteritis nodosa, and dermatomyositis. Side effects, not usually severe, include hypertension, glycosuria, and effects of cortical hyperactivity (Cushing's syndrome).

DRUGS INFLUENCING BLOOD-CELLS

Phenylhydrazine Hydrochloride (B.P.C.).

Dose.—*Orally:* **0·1 to 0·45 G (1½ to 7 gr.) in capsules.**

ACTIONS AND USES

Phenylhydrazine is destructive to erythrocytes and has been used in polycythæmia, but its hæmolytic effects must be controlled by blood estimations as its actions last at least a week and its safety margin is small. Initial doses of 0·1 G (1½ gr.) may be given twice or thrice daily for 10 days followed by an interval, but the aim should be to establish a weekly maintenance dose (about 0·1 to 0·3 G) based upon the effects on the blood count. Acetylphenylhydrazine (0·1 G daily) is said to be less toxic.

Injectio Nucleotidi (B.P.C.).—Liquor Pentosi Nucleotidi. Pentnucleotide. A sterile solution containing about 8% of Sodium Pentose Nucleotide.

Dose.—*Intramuscularly:* **10 to 20 Mils (150 to 300 min.)**

ACTIONS AND USES

Nucleotides increase the numbers of the granulocytes usually within 3 to 5 days and appear to hasten their production, but the responses to them are not constant. The Injection of Sodium Pentose Nucleotide is made deeply in the gluteal region twice daily for four or five days, and then once or twice weekly, in cases of agranulocytosis which have not improved by Penicillin treatment; the injections are painful and they may cause fever, cardiac pain and bradycardia with dyspnœa from impaired A-V conduction.

Nitrogen Mustards.—*Trio*-(β-chloro-ethyl)-amine hydrochloride and methyl-*bis*-(β-chloro-ethyl)-amine hydrochloride.

Dose.—*Intravenously:* **0·1 to 0·2 mg per Kg. body weight in 30 Mils of sterile saline.**

ACTIONS AND USES

These have been used in treating Hodgkin's disease and other forms of lymphosarcoma. Injections are given daily or on alternate days for 3 to 6 doses and are then regulated and spaced by their effect on the erythrocyte and leucocyte counts. These alkalamines are palliative by lowering the total white-cell count and decreasing the enlargement of the lymph nodes, spleen, and liver, but the effects seem to decline later. Chronic myeloid leukæmia and Hodgkin's disease respond best; chronic lymphatic leukæmia least; mycosis fungoides has been improved, and some benefit attained in anaplastic lung cancer. The injections are liable to cause local thrombosis and vomiting is a common sequel.

Folic Acid Antagonists.—Folic Acid is essential for the growth of normal cells, but related compounds, e.g. 4-amino-pteroylglutamic acid (Aminopterin) and amino-pteroylaspartic acid, have a powerful anti-folic-acid activity. They inhibit the multiplication of tissue cells and have a leucotoxic power which has effected temporary improvement in leukæmias; they have been shown to have a retarding action on some animal tumours and, if less toxic compounds become available, they may prove useful in human malignant diseases.

THE PITUITARY BODY

The pituitary body is a stalk of brain tissue (infundibulum) from the tuber cinereum, which forms the posterior lobe; the pars intermedia and the anterior lobe are developed from the back of the mouth.

Anterior Lobe.—This contains three types of cell:

(1) *Chromophobe Cells,* which may influence indirectly the other functions of the anterior lobe.

(2) *Eosinophil Cells,* which yield a hormone **promoting growth**; deficiency of it produces infantilism or dwarfs; over-secretion before the epiphyses are united in the young results in gigantism and in adults leads to premature old age or acromegaly.

(3) *Basophil Cells,* which are concerned with the secretion of several important controlling hormones:

Gonadotrophic or Sex Hormones.—The secretion contains a follicle-stimulating hormone (F.S.H., Prolan A) and a luteinising hormone (L.H., Prolan B).

In the male, the follicle-stimulating hormone controls spermatogenesis; and the luteinising hormone controls the external secretion (testosterone) of the interstitial cells of the testis.

In the female, the follicle-stimulating and luteinising hormones act together in influencing sexual developments at puberty, and in controlling the ovarian cycle and ovulation. The follicle-stimulating hormone increases the size and numbers of the ovules, and the production of the ovarian hormone, Œstradiol, which produces œstrus in animals and maturation of the uterus. The luteinising hormone stimulates the formation, growth and continuance of the corpus luteum and the production of the corpus luteum hormone, Progesterone, which excites progestational development of the uterine mucosa to favour implantation of the ovum.

The follicle-stimulating hormone can be obtained from the urine of non-pregnant and pregnant women; the luteinising hormone is found in the placenta and in the urine of pregnant women, its presence in their urine forms the basis of the **Aschheim-Zondek test** for pregnancy, namely, if doses of 0·2 to 0·4 c.c. of such urine be injected into immature female mice twice daily for three days, there appear in the ovaries of the mice enlarged follicles filled with blood and also corpora lutea.

Prolactin (Physolactin—*Dose*, 5, 5, 2, 2, 1 Mil on successive days intramuscularly), an anterior lobe hormone, initiates the secretion of milk in the mammary gland which has hypertrophied during pregnancy in response to stimulation by Œstrone and Progesterone.

The **Thyrotrophic Hormone** increases the vascularity of the thyroid gland, the output of thyroxine and, therefore, the basal metabolic rate.

There are also present an **Adreno-corticotrophic Hormone** which maintains the normal activity of the suprarenal cortex and a **Diabetogenic** and **Ketogenic Hormone** which produces glycosuria and ketosis.

Uses of Anterior Pituitary Extracts.—Dried whole or anterior pituitary gland by mouth and extracts of anterior lobe hypodermically have been tried in infantilism, but without producing uniform improvement.

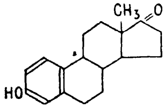
Extracts containing the follicle-stimulating hormone and also the luteinising hormone have been replaced by one or other of the Gonadotrophins or ovarian hormones.

Pars Intermedia and Posterior Lobe.—The cells of the pars intermedia secrete the hormone which enlarges the melanophores in amphibia. The posterior lobe provides two important hormones: (1) Vaso-pressin (Pitressin), which contracts the arterioles and other involuntary muscles, is antidiuretic, and antagonizes Insulin; (2) Oxytocin (Pitocin), which stimulates uterine muscle. The detailed actions of Pituitrin will be considered later (*see* p. 248). One must note here, however, that deficiency of the posterior lobe secretion produces obesity, which explains the fact that, if the secretions of both anterior and posterior lobes are deficient, a condition, termed Fröhlich's syndrome or dystrophia adiposo-genitalis, of infantilism associated with obesity results.

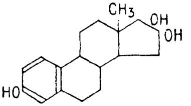
OVARIAN HORMONES

The ovary secretes two types of hormones:

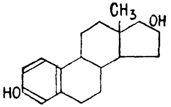
(1) **Œstrone, Œstriol and Œstradiol.**—Three important œstrus-producing sterols have been isolated: (*a*) Œstrone (ketohydroxy-œstrone), which occurs in the urine of pregnancy; (*b*) Œstriol (trihydroxy-œstrone) in the urine during pregnancy and in the placenta; and (*c*) Œstradiol (dihydroxy-œstrone), which is the true hormone secreted into the follicular fluid of the ovary and which also occurs in pregnancy urine. The benzoylated compounds of these hormones have a more prolonged action.



Œstrone



Œstriol



Œstradiol

Ovarian Menstrual Cycle.—In women, Œstradiol controls the follicular phase of menstruation. In the menstrual cycle, the first three or four days of bleeding (due to shedding of the endometrium) are followed by a period of rest. About the eighth day, Œstradiol, secreted increasingly as the Graafian follicle matures, excites the uterine endometrium to proliferation, and straight and spiral tubular glands, lined by columnar epithelium, develop and the mucosal blood-vessels dilate. From about the thirteenth day, when ovulation occurs, the further development (progestational or premenstrual) of the endometrium is due to Progesterone (the Corpus Luteum hormone) which prepares the endometrium to receive the ovum. After the fifteenth day, the epithelial cells of the glands become filled with mucus secretion and the gland walls become folded or crenate. If the ovum is fertilized, the persistence of Progesterone secretion continues the proliferation of the endometrium and aids the embedding of the ovum. But if the ovum is not fertilized, the stoppage of the Progesterone secretion about the twenty-eighth day, when the follicle degenerates, results in the shedding of the endometrium and a return of menstruation.

Œstronum.—Œstrone. 3-hydroxy-17-keto-$\Delta^{1:3:5}$-œstratriene.

CHARACTERS.—Colourless crystals, sparingly soluble in water, soluble in fixed oils. Prepared from the urine of certain animals. 1 Mg contains 10,000 Units of œstrogenic activity (œstrone standard).

Dose.—*Daily:* **Metric, 1 to 10 mg; Imperial, 1/60 to 1/6 gr.**

Preparation

Tabellæ Œstroni.—1 mg (1/60) in each.

Œstradiolis Dipropionas.—Œstradiol or Estradiol Dipropionate. α-3:17-dipropionoxy-$\Delta^{1:3:5}$-œstratriene.

CHARACTERS.—Colourless crystals, insoluble in water, soluble in fixed oils.

Dose.—*Daily; by intramuscular injection:*
Metric, 1 to 5 mg; Imperial 1/60 to 1/12 gr.

Preparation

Injectio Œstradiolis Dipropionatis.—A sterile solution for intramuscular injection in Ethyl Oleate or a suitable oil. 1 mg (1/60 gr.) in 1 Mil (15 min).

Œstradiolis Monobenzoas.—Œstradiol or Estradiol Monobenzoate α-3-benzoyloxy-17-hydroxy-$\Delta^{1:3:5}$-œstratriene.

CHARACTERS.—Colourless crystals, insoluble in water, soluble in fixed oils. 1 mg contains 10,000 Units of œstrogenic activity (benzoate standard).

Dose.—*Daily, by intramuscular injection:*
Metric, 1 to 5 mg; Imperial, 1/60 to 1/12 gr.

Preparation

Injectio Œstradiolis Monobenzoatis.—A sterile solution for intramuscular injection in Ethyl Oleate or a suitable oil, 1 mg (1/60 gr.) in 1 Mil (15 min.)

Stilbœstrol.—Diethylstilbœstrol. 4 : 4′-dihydroxy-α-β-diethylstilbene.

CHARACTERS.—Colourless crystals or powder, slightly soluble in water.

Dose.—*Daily:* **Metric, 0·5 to 2 mg; Imperial, 1/120 to 1/30 gr.**

Preparation

Tabellæ Stilbœstrolis.—0·5 mg (1/120 gr.) in each.

Hexœstrol.—Hexœstrol. *meso*-$\gamma\delta$-bis-(4-hydroxyphenyl)-*n*-hexane.

CHARACTERS.—Colourless crystals or powder, almost insoluble in water.

Dose.—*Daily:* **Metric, 1 to 5 mg; Imperial, 1/60 to 1/12 gr.**

Preparation

Tabellæ Hexœstrolis.—1 mg (1/60 gr.) in each.

Dienœstrol.—Dienœstrol. 4 : 4′dihydroxy-$\gamma\delta$-diphenyl-$\beta\delta$-hexadiene.

CHARACTERS. colourless crystalline powder, almost insoluble in water.

Dose.—*Daily:* **Metric, 0·1 to 5 mg; Imperial, 1/600 to 1/12 gr.**

Preparation

Tabellæ Dienœstrolis.—0·1 mg (1/600 gr.) in each.

ACTIONS AND USES

The natural Œstrogenic hormones are Œstradiol (the ovarian follicular hormone), Œstrone and Œstriol, all of which can be isolated from human pregnancy urine and the placenta. Œstrone, given orally, acts rapidly but is soon excreted; Œstriol, given orally, although acting rapidly, is the least potent; Œstradiol, given intramuscularly, is less rapid in action but about four times more potent than Œstrone.

The benzoates and dipropionates of Œstradiol have a longer action; thus Œstradiol Monobenzoate, injected intramuscularly, commences to act soon but its maximal effect occurs in from one to two days, and the action subsides in about five days; therefore two weekly doses may suffice for treatment.

The synthetic Œstrogens are Stilbœstrol, Hexœstrol and Dienœstrol, all of which are effective when given orally in the form of tablets. Stilbœstrol is usually prescribed, but it commonly causes nausea and malaise. Hexœstrol and Dienœstrol, formerly regarded as more potent, are about 3 to 5 times less active than Stilbœstrol. Ethinyl-Œstradiol is more satisfactory.

There is considerable variation in the results obtained from Œstrogens in treatment; it is recognized that these variations depend on differences in dosage, absorbability, and methods of administration, as well as upon the susceptibility of the tissues.

Actions.—The Œstrogenic hormones have the following actions: (1) they promote at puberty the maturation of the genital tract, and the development of the secondary sex characters; (2) they increase the development of the mammary gland and its ducts; (3) they excite endometrial proliferation in the preovulation phase of the ovarian cycle; (4) they sensitize the uterine muscle to Oxytocin and Progesterone; (5) they augment the tone of the uterine muscle and can excite contractions; (6) they check lactation, probably by inhibiting Prolactin.

Uses.—The Œstrogens are used to treat the following conditions: (1) retarded puberty, hypoplasia of the uterus, primary amenorrhœa and vaginitis before puberty; (2) sterility from uterine hypoplasia, when they are given during the first 10 to 14 days of the ovarian cycle; (3) anovulatory sterility, when "Œstrone shock" of the pituitary is produced by giving 5 mg (1/30 gr.) of Stilbœstrol 17 to 14 days before a menstrual period; (4) metropathia hæmorrhagica; (5) primary uterine inertia, both as prophylactics given in one daily dose during the last month of pregnancy, and also as treatment in hourly doses of 15 mg (1/10 gr.) of Stilbœstrol; (6) intra-uterine fœtal death, when 5 mg (1/30 gr.) doses of Stilbœstrol are given every four hours for four days to sensitize the uterus to Oxytocin and excite expulsive contractions; (7) mastodynia and to check lactation; (8) menopausal vasomotor and mental symptoms; senile vaginitis and kraurosis vulvæ.

Choice of Preparation.—Œstrone may be given orally in tablets or be injected intramuscularly in oily solution; if a local effect only is desired, it may be used by inunction in a cold cream, e.g. for mastodynia, or be incorporated in pessaries, e.g. for vaginitis.

Œstradiol Diproprionate and Monobenzoate are given intramuscularly in oily solution; they are absorbed relatively slowly from the injection area, reach a maximal effect in about two days and the action subsides in five or six days; two weekly doses may suffice for treatment. Œstradiol Monobenzoate, being more soluble in cold creams, is better than Œstrone for local inunction.

Stilbœstrol is the most commonly used Œstrogen, and 1 mg, given orally in tablet form, equals the effect of 0·5 mg. Œstradiol Monobenzoate by injection. For most purposes, doses of 0·5 to 1 mg (1/120 to 1/60 gr.) daily are used, but larger doses are necessary to stimulate the muscular activity of the uterus, and 2 mg (1/30 gr.) thrice daily for three or four days are required to check lactation.

Dienœstrol and Hexœstrol are about three or five times less potent than Stilbœstrol, but are less liable to cause nausea, even in the larger doses required to produce the same action.

During the menstrual period of life, the Œstrogenic hormones, should be administered only during the first 10 to 14 days of the ovarian cycle, and then in careful dosage, because, by proliferating the endometrium, withdrawal bleeding may result.

Œstrogens in prostatic carcinoma.—In prostatic carcinoma, the cells which have developed malignancy have a high acid phosphatase content; they can be caused to atrophy by reducing the androgenic hormone, e.g. by castration, or, more easily, by administering œstrogens which within five days will lessen the acid serum phosphatase level. It is usual to start treatment with

Stilbœstrol Dipropionate in dose of 5 to 10 mg (1/12 to 1/6 gr.) given as the Intramuscular Injection for 5 to 10 days and then to continue with maintenance doses of Stilbœstrol (or a substitute) in dose of 1 mg (1/60 gr.) orally twice or thrice daily for two or three months; but oral Stilbœstrol or Ethinyl-Œstradiol alone may be adequate. Symptomatic improvement follows rapidly, pain and œdema are reduced, micturition becomes less frequent and bony metastases show regression. Mastodynia may occur and necessitate smaller dosage.

Œstrogen therapy may ameliorate the late stages of malignant disease, e.g. breast cancer; Œstrogens may cause healing of ulceration in primary malignant growths and regression of metastasis in the skin and viscera, but have usually less effect on skeletal metastasis. If used before the menopause, they may aggravate the disease; after the menopause, they are liable to cause uterine hæmorrhage. They are of benefit also in breast cancer in males, although androgens are not.

Ethinyl-Œstradiol.—Estigyn. Lynoral.

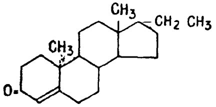
Dose.—Orally, in tablets: 0·05 mg (1/1,200 gr.).

ACTIONS AND USES

Ethinyl Œstradiol does not cause nausea or malaise, but it is about 10 to 50 times more potent than Stilbœstrol; it is used for the same clinical conditions.

For uterine hypoplasia with amenorrhœa or dysmenorrhœa, 0·05 mg is given thrice daily during the preovulation phase; similar dosage is effective in the treatment of menopausal symptoms. It has a powerful inhibitory effect on the anterior pituitary and doses of 0·05 mg daily relieve mastodynia, while this dose given six times daily during three or four days usually suffices to suppress lactation. It is also used, like Stilbœstrol, for the treatment of prostatic carcinoma.

Progesteronum.—Progesterone. 3 : 20-diketo-Δ^4-pregnene. Prepared from the corpora lutea of sows or other mammals, or from stigmasterol, pregnanediol or cholesterol.



Progesterone

CHARACTERS.—Colourless crystals, insoluble in water, soluble in fixed oils. 1 mg contains 1 Unit of specific progestational activity.

Dose.—*Daily, by intramuscular injection:* **Metric, 2 to 20 mg; Imperial, 1/30 to 1/3 gr.**

Preparation

Injectio Progesteroni.—A sterile solution in Ethyl Oleate or a suitable oil. Contains 5 mg (1/12 gr.) in 1 Mil (15 min.).

Æthisteronum.—Ethisterone. Pregneninolone. Anhydrohydroxyprogesterone. 17-ethinyl-Δ^4-androsten-17-ol-3-one.

CHARACTERS.—A white or cream crystalline powder, tasteless; insoluble in water.

Dose.—*Daily:* **Metric, 5 to 25 mg; Imperial, 1/12 to 2/5 gr.**

Preparation

Tabellæ Æthisteroni.—5 mg (1/12 gr.) in each.

Progesterone, the corpus luteum hormone, occurs also in the placenta and in the adrenal cortex; the placental source contributes to its action during pregnancy. Progesterone is converted into the inactive pregnanediol which is conjugated with glycuronic acid in the liver and excreted in the urine as the sodium salt. During pregnancy its amount increases rapidly from the third to the eighth month, but declines suddenly about ten days before the onset of labour.

Actions.—Progesterone will produce the following effects: (1) it inhibits œstrous ovulation and menstruation; (2) it is responsible, after ovulation, for the pregestational proliferation of the œstrogenized endometrium and thus prepares it for the embedding of the ovum; (3) if the ovum is fertilized, it promotes the growth of the placenta; (4) it induces uterine quiescence and reduces uterine tone by inhibiting the action of Oxytocin, the movements being less frequent but somewhat larger; (5) it stimulates hypertrophy of the acini of the mammary gland.

Uses.—Progesterone is employed in the treatment of (1) uterine hypoplasia, primary amenorrhœa and anovulation; the doses are given during the pregestational phase of the ovarian cycle and are usually preceded by a preovulation course of an Œstrogen; (2) secondary amenorrhœa, dysmenorrhœa and sterility from lack of luteal hormone, given from the twelfth or eighth to the fifth day before menstruation is expected; (3) metropathia hæmorrhagica, when 10 mg are given daily, but withdrawal bleeding may occur from the stimulated endometrium; (4) threatened and habitual abortion, if the excretion of pregnanediol is low: in threatened abortion, 10 mg daily is given until a week after hæmorrhage ceases; in habitual abortion, 10 mg twice weekly is given from a month before, until two or three months after, the expected time of abortion; (5) after-pains, for which 1 mg is given six hours after birth to reduce the uterine contractions and is repeated when necessary.

Ethisterone, which is given orally, has the same actions and uses as Progesterone; the comparative potency is that 5 to 10 mg of Ethisterone have the equivalent action of 1 mg of Progesterone given intramuscularly. It is therefore largely used in order to avoid frequent intramuscular injections.

Gonadotrophinum Chorionicum.—Chorionic Gonadotrophin. A sterile preparation containing the gonad-stimulating substance from the urine of pregnant women, prepared by alcoholic precipitation of the urine at *p*H 5.

CHARACTERS.—A white or fawn powder, soluble in water. The container label gives the number of Units and the date of manufacture.

Assay.—The potency must equal the gonadotrophic activity of the Standard Preparation which contains 1 Unit in 0·1 mg. The activity is estimated by the increase in weight produced in the ovaries of immature female rats from an unstimulated level of about 10 mg to a maximum of about 40 mg.

Storage.—If kept not above 20° C., it retains its potency for 12 months.

Dose.—*By intramuscular injection:* **100 to 500 Units.**

Preparation

Injectio Gonadotrophini Chorionici.—A sterile solution for intramuscular injection in Water for Injection, containing 0·5% Phenol, made immediately before use.

ACTIONS AND USES

Chorionic Gonadotrophin from human pregnancy urine corresponds in action with the luteinizing hormone (L.H.) of the anterior pituitary; it stimulates the internal secretions of progesterone and testosterone.

In women, it has been used in metropathia hæmorrhagica in doses of 100 to 500 Units daily; and in the prevention and treatment of habitual and threatened abortion, although here its effects are not reliable. In males, it increases the secretion of testosterone and stimulates development of the secondary sex characters; for undescended testes, doses of 500 Units are given twice weekly for a period of four to six weeks. Adolescent acne is treated by injecting 200 Units twice or thrice weekly.

Gonadotrophinum Sericum.—Serum Gonadotrophin. A sterile preparation containing the follicle-stimulating substance from the serum of pregnant mares, prepared by fractional precipitation with alcohol from the blood plasma, taken between the 60th and 75th days of pregnancy.

CHARACTERS.—A white powder, soluble in water. The container label states the number of Units and the date of manufacture.

Assay.—The potency must equal the gonadotrophic activity of the Standard Preparation which contains 1 Unit in 0·25 mg. The activity is estimated by the increase in weight produced in the ovaries of immature female rats from an unstimulated level of about 10 mg to a maximum of about 220 mg.

Storage.—If kept not above 20° C. it retains its potency for 12 months.

Dose.—*By intramuscular injection:* **200 to 1,000 Units.**

Preparation

Injectio Gonadotrophini Serici.—A sterile solution for intramuscular injection in Water for Injection, containing 0·5% Phenol, prepared immediately before use.

ACTIONS AND USES

Serum Gonadotrophin from pregnant mares' serum has the actions of the follicle-stimulating hormone (F.S.H.) of the anterior pituitary. It stimulates the development of the ovarian follicle and of the seminiferous tubules; it does not of itself excite ovulation which may depend on an alteration in the ratio of F.S.H. to L.H. factors.

It is given for delayed puberty and amenorrhœa in doses of 500 Units thrice weekly, sometimes along with an Œstrogen; and for anovulation, in doses of 200 Units thrice weekly during the preovulation phase of the menstrual cycle, followed by Chorionic Gonadotrophin on alternate days until just before menstruation is due. In male sterility from deficiency of spermatozoa, 400 Units twice weekly have been given for a period of three months.

Testosteroni Propionas.—Testosterone Propionate. 17-propionoxy-Δ^4-androsten-3-one. Testosterone may be prepared from testes tissue or from dehydro*iso*androsterone.

CHARACTERS.—A white or cream crystalline powder; almost insoluble in water, soluble in fixed oils.

Dose.—*Daily, by intramuscular injection:*
Metric, 5 to 25 mg; Imperial, 1/12 to 2/5 gr.

Preparation

Injectio Testosteroni Propionatis.—A sterile solution in Ethy Oleate or a suitable oil. Contains 10 mg (1/6 gr.) in 1 Mil (15 min.)

Methyltestosteronum.—Methyltestosterone. 17-methyl-Δ^4-androsten-17-ol-3-one.

CHARACTERS.—A white or cream crystalline powder; almost insoluble in water, soluble in fixed oils.

Dose.—*Daily, orally:*
Women: **Metric, 5 to 20 mg; Imperial, 1/12 to 1/3 gr.**
Men: **Metric, 25 to 50 mg; Imperial, 2/5 to 3/4 gr.**

Preparation

Tabellæ Methyltestosteroni.—5 mg (1/12 gr.) in each.

ACTIONS AND USES

Testosterone Propionate has the actions of the hormone testosterone, but is more suitable than this for treatment as it is more soluble in oils and has a longer action; it stimulates development of the secondary sex characters but not spermatogenesis.

It has been used in delayed puberty, sexual under-development, and cryptorchidism in youths, for impotence, and in the prostatic hypertrophy of the aged, when it may mitigate symptoms if it does not reduce the hypertrophy. In atrophic rhinitis, it improves the vascularity of the nasal mucosa, and because of its vaso-dilator action it has been advised in angina pectoris and thrombo-angiitis obliterans.

In women, it has been given to check excessive pituitary activity which causes undue œstrogen formation, and thus it decreases metropathia hæmorrhagica and also through the pituitary it inhibits lactation and relieves mastodynia.

Methyltestosterone is most effectively absorbed sublingually, and the Tablet is a convenient form for the maintenance of treatment of testosterone deficiencies.

Androgens are effective in controlling visceral and particularly skeletal metastasis in late stages of malignant disease, and may be used for young and old patients of both sexes. They give relief from pain, cutaneous ulcers may heal and the weight often increases. From 150 to 300 mg. of Testosterone Proprionate are given daily by intramuscular injection to a total of 3,000 to 6,000 mg, and, if improvement occurs, an implant of 3,000 mg may be made.

DRUGS ACTING MAINLY ON THE HEART

Cardiac tonics are drugs that improve the functional activity of the heart in diseased conditions. They act partly by an influence on the nervous mechanism of the heart and partly by stimulating the heart muscle. To this class belong Digitalis, Strophanthus, Ouabain and Squill.

Digitalis Folium.—Digitalis Leaf. Foxglove Leaves. The leaves of Digitalis purpurea. N.O. Scrophularineæ, dried rapidly soon after collection at a temperature between 55° and 60° C.

CHARACTERS.—Broadly ovate, dull-green, hairy leaves with a winged petiole and crenate margin. Odour faint; taste very bitter.

COMPOSITION.—The active principles of Digitalis are **glycosides**; (1) *Digitoxin*, $C_{41}H_{64}O_{13}$, which hydrolyzes into the aglucone, digitoxigenin, $C_{23}H_{34}O_4$, and digitoxose, is the most active; (2) *Gitoxin*, $C_{41}H_{64}O_{14}$, *which splits into the aglucone, gitoxigenin,* $C_{23}H_{24}O_5$ and digitoxose: both of these glycosides are crystalline, insoluble in water but soluble in chloroform; and (3) *Gitalin*, $C_{35}H_{56}O_{12}$. Other glycosides, amorphous but more soluble in water and of uncertain composition, are present.

Biological Assay of Digitalis.—The International Unit is the activity of 80 mg of a Standard dry Digitalis powder. The activity may be assayed (1) on frogs, by preparing with alcohol a 10% extract of the powder and determining the amount of the extract in Mils (about 0·5 Mil, i.e. 1/2 Unit) which is required to produce death by systolic standstill of the ventricle per 100 G frog within 24 hours. The potency of an unknown powder is assessed by comparing, with that of the Standard, the percentage mortality amongst the frogs. (2) On cats or guinea-pigs, by injecting slowly into a vein extracts of specified strength while the animals are under anæsthesia and artificial respiration, and determining the amount required to arrest the heart in comparison with that used of the Standard. 1 Mil of a 10% standard Tincture per Kg arrests the heart in cats (i.e. 1 Cat Unit).

Digitalis Præparata.—Prepared or Powdered Digitalis. Digitalis Leaf in moderately coarse powder. Standardized to contain in 1 G 10 Units of activity. 0·1 G (1½ gr.) contains 1 Unit of activity.

Dose.—Metric, 30 to 100 mg; Imperial, 1/2 to 1½ gr.

Preparations

1. **Tabellæ Digitalis Præparatæ.**—60 mg (1 gr.) in each, or 0·6 Units.
2. **Tinctura Digitalis.**—Tincture of Digitalis. Prepared from Digitalis Leaf or Prepared Digitalis 80 to 100 G (1000 Units) with Alcohol 70% to 1000. Standardized to contain in 1 Mil (15 min) 1 Unit of activity.

Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

ACTIONS AND USES

Externally.—The glycosides of Digitalis leaf, if applied to a raw surface or mucous membrane, are irritants; for this reason and the fact that the pure glycosides are insoluble in water, preparations of Digitalis leaf cannot be given by hypodermic or intravenous injection.

Internally.—Digitalis is irritant in the stomach: dyspepsia, nausea or vomiting, followed by diarrhœa, often occur shortly after administration of full doses; but delayed nausea and vomiting result from cumulation of digitoxin stimulating the vomiting centre.

The glycosides of Digitalis are absorbed slowly, therefore the action develops gradually, and, as digitoxin is very slowly excreted, the action is maintained for some days. Digitalis **exerts its principal effects on the circulatory system**; but differences exist between its actions in the lower animals and in man, as well as on normal and diseased hearts respectively.

(i) *Frogs.*—Digitalis acts even after the vagal endings have been paralysed by Atropine; therefore, in frogs, it acts directly on the heart. It (1) depresses the rhythmogenic area, hence the sinus, auricles and ventricle beat more slowly; and (2) lowers the auriculo-ventricular conductivity so that the ventricle fails to respond to each auricular beat. Later (3) the systole is augmented and relaxation rendered less complete (increased tone). Finally, standstill occurs with the ventricle in firm systole but with the auricles dilated.

(ii) *Mammals.*—Given by injection, the action of Digitalis on the mammalian heart is double: (*a*) it stimulates the vagus centre in the medulla, and to a slight extent the vagus terminations; (*b*) it stimulates the cardiac muscle. The progressive effect depends on the predominance of one or other of these factors.

In the *first stage* there is vagal stimulation associated with moderate muscular stimulation. The heart is slowed by prolongation of diastole, and relaxation is more complete. The strength and amplitude of the systole are increased owing to direct stimulation and increased excitability of the cardiac muscle. The effect is to increase the volume of blood discharged at each beat and to augment the blood-pressure. With increasing dosage, Digitalis stimulates the vasoconstrictor centre and also, directly, the muscle of the arterioles, and these actions contribute towards the rise in blood-pressure. Still larger doses are required before the renal vessels constrict; therefore, at first, these undergo passive dilatation and the more efficient circulation through them leads to an increased secretion of urine. This corresponds with the *therapeutic stage* in man.

In the *second stage*, because the vagus stimulation predominates over the muscular stimulation, the heart-beat becomes still slower, hence the output of the ventricle per minute decreases—and the blood-pressure falls. Because vagus stimulation diminishes the conductivity of the auriculo-ventricular bundle, arrhythmia may occur, and the ventricle may show dropped beats, partial heart-block, or may adopt its own rhythm. In this stage, the vasoconstricting actions of Digitalis is exerted upon the renal vessels also, hence, from the reduced blood-flow through the kidney, less urine is secreted.

In the *third stage* the excitability of the muscle is increased so much that it escapes from the vagus control; the rate of the heart becomes much more rapid, and the blood-pressure increases temporarily; but soon the rapid contractions become irregular in force and frequency, and the blood-pressure shows wide and frequent variations; thus the circulation begins to fail. Later, the A-V conduction is depressed by a direct action of Digitalis on the conducting bundle; extra-systoles from stimulation of subsidiary rhythmic centres appear; finally, auricular and then ventricular fibrillation occur; and the heart stops in diastole.

Digitalis stimulates the respiratory centre to a slight extent and renders breathing more rapid; vomiting, due to stimulation of the medullary centre, also occurs if the dosage be excessive. Digitalis increases the tone of involuntary muscles, such as the gastro-intestinal, bronchial and uterine muscle.

(iii) *Man.*—Digitalis glycosides, being insoluble in water, are *slowly absorbed*; when given by mouth in ordinary doses the action begins only after 24 to 48 hours, and is fully developed in 4 to 5 days; by using large initial doses of the Tincture, such as 2 fl. dr. twice and 1 fl. dr. twice at six-hourly intervals, the cardiac effects will commence in about 6 hours and be fully developed in 24 hours (*see* p. 236).

The **rate of the heart is distinctly slowed** by prolongation of diastole. This results from **stimulation of the vagus centre**, which diminishes the output of stimuli from the rhythmogenic area at the junction of the sinus and auricle. This vagal stimulation also **reduces the conductivity** of the cardiac muscle and **of the A-V bundle of His** so that the rhythmic stimulus is delayed in its passage from the auricle to the ventricle with consequent lengthening of the auriculo-ventricular (P-R) interval in electrocardiograms.

At the same time, the **force of the systole is increased by direct muscular stimulation**, and the tone of the myocardium is improved so that the præcordial impulse becomes stronger and the first sound louder and more crisp in tone. The results are that, owing to the lengthened diastoles, the veins are more effectively drained, the venous pressure falls and the ventricles are better filled; also, by the improved systoles, the ventricles are thoroughly emptied; therefore, the arteries are better filled (increased output) and the pulse, although less frequent, has an improved systolic pressure and amplitude. The increased muscular irritability is probably the cause of the reversal of the T-wave in electrocardiograms. In man the **blood-pressure is not raised** by Digitalis because, owing to his more highly organized vasomotor control, the effect of the increased cardiac output is adjusted by splanchnic dilatation. No arterial constriction occurs, as the amount of Digitalis which causes this action is much in excess of the therapeutic dose for the heart. Digitalis **increases the amount of urine**—mainly of the water—only if it improves the cardiac efficiency, because this will increase the blood-flow through the kidney in a unit of time. These are the desirable therapeutic effects of Digitalis.

Cumulative Effects.—About 1 to 1·5 Mils or Units (15 to 22 min.) of Tincture of Digitalis are excreted or destroyed each day by the body; therefore continued large doses produce symptoms of cumulation. These are: (*a*) from medullary stimulation, nausea and vomiting; (*b*) from less efficient circulation, reduction in the quantity of urine; (*c*) from excessive vagal stimulation, bradycardia, dropped ventricular beats or heart-block removable by Atropine; (*d*) from direct depression of A-V conductivity, arrhythmia, dropped beats, pulsus alternans or heart-block not removable by Atropine; (*e*) from hyperexcitability of the muscle, extra-systoles, coupled beats, tachycardia and auricular fibrillation. Such symptoms subside if the dosage be reduced.

Therapeutic Uses.—It should be noted that the existence of a cardiac lesion is not primarily an indication for Digitalis. If the circulation remains efficient, or can be made so by restricting the patient's activities, treatment with Digitalis is unnecessary and may be harmful. In all cardiac deficiencies, its effects must be carefully watched because patients exhibit differences in reaction even to standardized preparations, and it is important that the dosage should be so adjusted as to produce the maximal benefit to the circulatory system in each case.

Rhythmic Disorders.—Digitalis is of great value in the treatment of **auricular fibrillation,** a condition in which there is no orderly beat of the auricle, but rapid and independent contractions—about 420 per minute—of its individual muscular fibres. These fibrillations lead to a series of inco-ordinate impulses being conveyed through the Bundle of His to excite the ventricle. In consequence the ventricular contractions become rapid (100 to 140 per minute) but irregular in time and strength; therefore, the ventricle becomes rapidly weakened and the circulation inefficient. The beneficial effect of Digitalis in auricular fibrillation is due to its action in depressing the conductivity of the Bundle of His, and thus, by establishing heart-block, Digitalis prevents most of the inco-ordinate auricular stimuli from reaching the ventricle. Under Digitalis the ventricle beats more slowly and regularly, the volume of the pulse is increased and an efficient pulmonary and peripheral circulation is restored; but the auricular fibrillation itself is not influenced by Digitalis.

In **auricular flutter** where the auricle beats very rapidly—about 300 per minute—but regularly, the ventricle often responds to each second beat. Digitalis, by increasing the muscular irritability, converts the flutter into fibrillation, but, by lowering A-V conductivity, slows the ventricle. If the drug be then stopped, fibrillation usually ceases and the pace maker restores the normal rhythm. For sinus arrhythmia, extra-systoles and febrile tachycardia, Digitalis is seldom useful, but it is suitable for paroxysmal tachycardia caused by deficient vagal control. In Adams-Stokes syndrome (heart-block) Digitalis obviously is contra-indicated.

Congestive Cardiac Failure in Valvular Disease.—The first principle in the treatment of valvular defects is rest and limitation of the patient's activities so as to avoid any strain upon the damaged heart. The heart muscle has considerable powers of compensating for valvular errors by hypertrophy but, if the resources of Nature are inadequate or from undue strain are overbalanced in their attempt to maintain an efficient circulation, a complex of symptoms termed "failure of compensation" results: the ventricular systole becomes weak and rapid, the volume and force of the pulse decline, and the veins are imperfectly drained so that partial stagnation of the blood occurs in the lungs and tissues; the oxygenation and nutrition of the tissues becomes imperfect, therefore breathlessness occurs upon slight exertion, the urinary secretion is reduced, and dropsy supervenes.

Under suitable doses of Digitalis, the slowing of the ventricle and its increased tone and systolic force lead to better filling of the heart from the veins and lungs, and to an improvement in the pulse. Consequently the venous pressure falls and pulmonary congestion with the attendant cyanosis and breathlessness are relieved, œdematous exudates are absorbed and, with the improved renal circulation, profuse diuresis sets in about the third day of treatment. When the heart muscle has recovered, dosage may be reduced or discontinued. Mitral incompetence and stenosis, tricuspid incompetence and aortic obstruction are the forms of valvular disease in which cardiac failure is most successfully relieved by Digitalis. In aortic incompetence, although it is ordinarily believed to be disadvantageous by lengthening diastolic reflux, Digitalis may be used if the ventricle fails: marked slowing of the pulse need not be a feature of its action here.

Myocardial Diseases.—Digitalis is useful in cardiac failure from muscular weakness. It may fail to produce slowing, but it strengthens the systole and reduces the relaxation by muscular stimulation, so that oxygenation of the heart is improved by the increased coronary blood-flow. Cases of fibroid and fatty degeneration of the cardiac muscle associated with arterial sclerosis are rarely improved, because Digitalis does not influence pathological tissues but invigorates only the sound muscle; when, however, circulatory failure occurs in such conditions, Digitalis is worthy of trial. Digitalis is often beneficial when the hypertrophied heart of chronic nephritis fails to overcome the increasing peripheral resistance. In the acute stages of inflammatory heart disease—myocarditis, pericarditis and endocarditis—Digitalis should be withheld as a rule; but if sudden weakening of the ventricular beat occurs, it should be tried; and when recovery from these diseases begins, small doses often prove beneficial.

Digitalis as a Diuretic.—The diuretic action is dependent upon functional improvement in the circulation, therefore it is not marked in normal subjects or in œdemas not due to circulatory failure. In cardiac œdema Digitalis acts as a powerful diuretic in proportion to the circulatory improvement.

Digitalis in Pneumonia.—Digitalis has been recommended to obviate the occurrence of cardiac failure in pneumonia but it is better to give Digoxin for a rapid effect if failure occurs.

The Reduction of Venous Pressure.—In man, as has been found in dogs, Digitalis glycosides can cause a fall in the right auricular venous pressure probably through an action on the venous tone. Starling proved that as the right auricular pressure rises, the cardiac output increases to a maximum, but that any further increase in venous pressure leads, from overload, to a fall in the ventricular output.

McMichael and Sharpey-Schafer have pointed out that cardiac failure with venous congestion falls into two groups: (1) Congestive failure *with a low output*, as in hypertensive, ischæmic or valvular heart disease, in which the heart behaves as if overloaded in that increase of venous pressure induces a fall in cardiac output, while a reduction in venous pressure leads to an improvement in cardiac output; and (2) failure *with a high output*, resulting from such conditions as deficient oxygen-carrying power of the blood in anæmia, or emphysema, metabolic defects (beri-beri), or mechanical overload, in which group the rise in venous pressure has been compensatory to maintain the cardiac output, and any decrease in venous pressure will lower the output.

The effect of Digitalis or Digoxin in these two groups differs: *In the low-output group,* Digoxin was found to reduce the venous pressure and to raise the cardiac output, as did also venesection or mechanical lowering of the pressure by cuffs applied to the thighs; and it is deduced that the venous-pressure-reducing action is primarily responsible for the improvements in low-output failure.

In the high-output group, Digitalis or Digoxin lowered the venous pressure and also lowered the cardiac output, as did also venesection; and this is found to be the response of the normal heart.

There is evidence from the product of the cardiac output and the mean arterial pressure that Digoxin does increase the work done by the heart, but that this stimulant action on the myocardium is weaker than that produced by Ouabain. The response of the heart to venous-pressure change is regarded as determining the effect of Digoxin on the cardiac output. With Ouabain, the muscle stimulant action seems to predominate, and the venous-pressure effect is weaker.

It is suggested that the fundamental actions of the cardiac glycosides are: (1) A venous-pressure-reducing action, most pronounced with Digoxin, which (*a*) lowers the output of a normal heart and the heart in "high-output" failure, but (*b*) raises the output in "low-output" failure. (2) A direct muscular stimulant action, seen only in certain types of failure, and possessed in greater degree by Ouabain than by Digoxin. (3) A rate-reducing action in auricular fibrillation which does not enhance the above actions.

It is difficult to accept the foregoing account as the full explanation in view of the influences which Digitalis has been proved to have both experimentally and clinically upon the heart itself and which afford explanations of its actions as well as of its toxic effects.

Principles of Dosage with Digitalis.—It has been estimated that the daily destruction and excretion of Tincture of Digitalis by an average adult (140 lb.) is from 1 to 1·5 Mils or Units (15 to 22 min.) and that 20 Mils or Units (5 fl. dr.) are required in the body to produce the full therapeutic effects, while 22 Mils or Units (5½ fl. dr.) may induce symptoms of over-dosage. These doses are based on Eggleston's estimation that the effective dosage of Tincture of Digitalis is 0·15 Mil (2½ min.) per lb. body weight. From these data it is possible to estimate when the full effective dosage will be reached by different methods of administration.

(*a*) **Intensive Course.**—This is used when a rapid action is desired. The effective dose of 20 Mils (5 fl. dr.) is given within a day, that is, 10 Mils (2½ fl. dr.) at once, reduced progressively every six hours, namely, 5 Mils, 2·5 Mils and 2·5 Mils. By this means effects commence within six hours, reach a maximum in 24 hours and persist without further dosage for about ten days.

(*b*) **Cumulative Course.**—This consists in giving from 1 Mil to 1·3 Mil (15 to 20 min.) every six hours until the full effects develop, which usually occurs between the fourth and sixth days.

Digitalis Præparata contains 1 Unit in 0·1 G (1½ gr.) and of it about 0·1 to 0·15 G (1½ to 2½ gr.) is destroyed or excreted daily. The corresponding effective dose for an adult of 10 stones would be 2 G (30 gr.) which can be given in four doses at 6-hourly intervals or, if given by the cumulative course, the 6-hourly dose would be 0·13 to 0·2 G (2 to 3 gr.).

When the full therapeutic effects have been attained it may be possible, if compensation is re-established in congestive cardiac failure, to discontinue the drug; but sometimes, and usually in auricular fibrillation, a maintenance dosage requires to be established, and this should not be less than 1 Mil (15 min.) of Tincture, or 0·15 G (2½ gr.) of Prepared Digitalis daily. The maintenance dose should not be started until the fourth day after full digitalization has been effected. Maintenance dosage may be so arranged that the Digitalis is taken only on certain days each week, the amount being regulated below that which causes headache or nausea.

Selection of Preparation.—The standardized Tincture of Digitalis and Digitalis Præparata are both very reliable preparations. Digitalis Præparata, when given in tablet form, may by irritation cause nausea or diarrhœa.

Digitoxinum (B.P.C.).—A mixture of the insoluble crystalline glycosides Digitoxin and Gitoxin, and more soluble glycosides.

Dose.—Metric, 0·1 to 1 mg; Imperial, 1/600 to 1/60 gr.

ACTIONS AND USES

Digitoxin is less likely to cause nausea and may be given in pills or, in 0·1% solution, it may be injected hypodermically but may cause irritation; it is very slowly excreted during a week or more, and is, therefore, cumulative.

Nativelle's Digitalin Granules consist chiefly of Digitoxin and are available for oral administration in doses of 1/600 and 1/240 gr.

Digoxinum.—Digoxin. $C_{41}H_{64}O_{14}$. A crystalline glycoside from the leaves of Digitalis lanata. N.O. Scrophularineæ, the Austrian or woolly-leaved foxglove (flowers yellow).

CHARACTERS.—Colourless, tabular crystals; taste bitter; almost insoluble in water.

Dose.—*Oral, initial:*
Metric, 1 to 1·5 mg; Imperial, 1/60 to 1/40 gr.
Oral, maintenance, once or twice daily:
Metric, 0·25 mg; Imperial, 1/240 gr.
By intravenous injection, initial:
Metric, 0·5 to 1 mg; Imperial, 1/120 to 1/60 gr.

Preparations

1. **Injectio Digoxini.**—This is prepared immediately before use by mixing a sterile alcoholic (70%) solution of Digoxin (0·05%) with 9 times its volume of Injection of Sodium Chloride. 20 Mils (300 min.) contain 1 mg (1/60 gr.).
Dose.—*By intravenous injection:*
Metric, 10 to 20 Mils; Imperial, 150 to 300 min.
2. **Tabellæ Digoxini.**—0·25 mg (1/240 gr.) in each.

ACTIONS AND USES

Digoxin is being used increasingly in place of the preparations of Digitalis for the treatment of congestive cardiac failure and auricular fibrillation as it acts rapidly and is conveniently given in the tablet form. It is very potent and the facts about its activity must be recollected: 1 mg (1/60 gr.) of Digoxin has a Digitalis activity of 3 Units; or, conversely, 1 Unit is contained in 0·3 mg (1/200 gr.) of Digoxin. The following are convenient approximate equivalents: 1 mg (1/60 gr.) of Digoxin, 0·3 G (5 gr.) of Prepared Digitalis, and 3 Mils (45 min.) of Tincture of Digitalis.

Digoxin has the actions of Digitalis but, being more quickly excreted, it is less liable to cause symptoms from cumulation; the initial symptoms are, however, those of Digitalis, namely, headache, lack of appetite and nausea. When given orally, it is absorbed rapidly and begins to slow the ventricle within one hour, the maximal effect is developed in six hours, and the former rate returns in about three days. If injected intravenously, it acts within ten minutes, the maximal effect is reached in one to two hours and the action lasts about two or three days. The Injection, or even a large initial dose orally, must not be given if the patient has been previously on Digitalis until its action has completely passed off; and care should be taken to avoid the Injection getting outside the vein as it is irritant; also it should be injected slowly.

Digoxin is a very satisfactory means of bringing the heart rapidly under Digitalis control and, after allowing time for the initial dosage to subside, a maintenance dosage can be arranged by prescribing the Tablet of 0·25 mg (1/240 gr.) twice daily or less frequently as the individual case may require.

Strophanthus.—Strophanthus Seeds. The dried ripe seeds of Strophanthus kombé. N.O. Apocynaceæ, freed from the awns.

CHARACTERS.—Flat, lanceolate, silky-haired, fawn seeds, ridged on one side.

COMPOSITION.—*K-strophanthin*, a mixture of glycosides.—*Cymarin*, *k-strophanthin* β, and an amorphous *strophanthin* which, on hydrolysis yield the aglucone strophanthidin, cymarose, and sugar; also kombic acid, choline, trigonelline, and fat.

Preparation

Tinctura Strophanthi.—Strophanthus 10; Alcohol 70% to about 100; by percolation with light petroleum to remove fat and subsequent percolation with Alcohol.

Standardized to be equivalent in activity to a 0·42% solution of International Standard Ouabain, estimated by the effect on the frog's heart as described for Digitalis. It has about 45 times the activity of Tincture of Digitalis.

Dose.—Metric, 0·12 to 0·3 Mil; Imperial, 2 to 5 min.

ACTIONS AND USES

Strophanthus resembles Digitalis in its actions but the Tincture differs from Tinctura Digitalis in these ways: (1) it is less irritant and therefore causes less gastric upset; (2) its glycoside is more readily destroyed in the stomach; (3) it is more rapidly absorbed and quicker in action; (4) it is a weaker medullary stimulant, causing less late nausea, less cardiac slowing, and less arterial constriction; (5) it is a better diuretic; and (6) it is more rapidly excreted, hence cumulation is rare. The Tincture influences the heart within one hour, therefore small doses are used and their effects observed carefully.

Ouabainum.—Ouabain. Strophanthin G. $C_{29}H_{44}O_{12},8H_2O$. A crystalline glycoside obtained from the seeds of Strophanthus gratus, N.O. Apocynaceæ, or from the wood of Acocanthera Schimperi, N.O. Apocynaceæ.

CHARACTERS.—A white crystalline powder, taste bitter. *Solubility.*—1 in 100 of water.

Dose.—*By intravenous injection:*

Metric, 0·12 to 0·25 mg; Imperial, 1/500 to 1/240 gr.

Preparation

Injectio Ouabaini.—A sterile solution in Water for Injection. Contains 0.25 mg (1/240 gr.) in 1 Mil (15 min).

ACTIONS AND USES

Ouabain has twice the potency of Strophanthin K (B.P. 1932). It is more soluble and is rapidly absorbed when given orally, but its action lasts a shorter time—about 24 hours—as it is more quickly excreted. It is usually injected intravenously, when it will influence the heart within a few minutes; further treatment, after 24 hours, being effected by Digitalis or Digoxin in maintenance doses.

Ouabain has been found to have only a slight effect in lowering venous pressure, but it increases the cardiac output and the arterial pressure; this is due to a stimulant action on the cardiac muscle which Digoxin has only to a lesser degree. In emphysematous failure, Ouabain tends to increase the cardiac output, whereas Digoxin usually lowers it. Ouabain is sometimes successful in cardiac disease when Digitalis has failed.

Scilla.—Squill. The bulb of Urginea maritima. N.O. Liliaceæ; divested of outer scales, cut into slices, and dried.

CHARACTERS.—Curved, yellowish, tapered strips; taste bitter.

COMPOSITION.—A crystalline glycoside *Scillaren A*, $C_{36}H_{52}O_{13}$, which on hydrolysis yields the aglucone scillaridin *A*, $C_{24}H_{30}O_3$, and rhamnose; and *Scillaren B*, a mixture of active glycosides.

Dose.—In powder: Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

Preparations

1. **Acetum Scillæ**, Vinegar of Squill.—Squill, 10% in Dilute Acetic Acid.
Dose.—Metric, 0·6 to 2 Mils; Imperial, 10 to 30 min.
2. **Syrupus Scillæ.**—Vinegar of Squill 45%, with Sucrose and Distilled Water.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
3. **Oxymel Scillæ.**—Squill 5%, with Acetic Acid, Honey and Distilled Water.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
4. **Tinctura Scillæ.**—Squill 10%, in Alcohol 60%.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.

ACTIONS AND USES

Squill **resembles Digitalis** in its action on the heart but its glycosides are more irritant to the stomach and less easily absorbed. The Tincture has less than half the cardiac potency of Tincture of Digitalis. The preparations of Squill have, therefore, a very restricted value in cardiac diseases because in adequate dosage they would cause nausea.

Squill is a useful **expectorant** because, from its irritant action on the stomach, it reflexly increases and liquefies the bronchial secretion. It is used mainly in chronic bronchitis where the indications are to improve the circulation and facilitate removal of viscid muco-purulent sputum. If prescribed with Ammonium Bicarbonate, the Tinctura Scillæ must be used as the other preparations are acid.

Squill is somewhat more powerfully **diuretic** than Digitalis and is useful in cardiac dropsy.

Quinidinæ Sulphas.—Quinidine Sulphate. $(C_{20}H_{24}O_2N_2)_2, H_2SO_4,2H_2O$. An alkaloidal salt, isomeric with Quinine, obtained from various species of Cinchona.

CHARACTERS.—Colourless, needle-like crystals, darkening in light; taste very bitter. *Solubility.*—1 in 90 of water.

Dose.—Metric, 60 to 300 mg; Imperial, 1 to 5 gr.

ACTIONS AND USES

Quinidine Sulphate in susceptible patients may cause symptoms of "quinism," e.g. headache, ringing in the ears, nausea, etc., therefore a small initial dose should be given.

Quinidine has direct effects upon cardiac muscle: it **increases the refractory period** of the muscle, diminishes its excitability and **slows the conduction** of the impulse both in the muscle and also, after large doses, through the A-V bundle; there results a slowing of the cardiac rhythm and an increased amplitude in the ventricular beat.

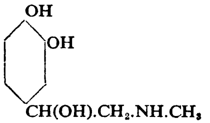
The value of Quinidine is in the **treatment of auricular fibrillation** where the lengthened refractory period renders the auricular muscle insusceptible to the excessively frequent waves or circuits of excitation; the rate of the auricle therefore declines rapidly, and a normal rhythm may be suddenly restored by the sinus pacemaker resuming control over the auricular rhythm. But only about 50 per cent. of cases respond because, since the drug also slows conduction, the waves circling round the auricle may be so slowed in transmission that by the time they have completed the circuit, the refractory period will have passed off.

In treatment it is usual to give doses of 0·2 G (3 gr.) in tablet form increasing from 3 to 10 doses daily. From electro-cardiograms it can be seen that the auricular rate of about 400 slows down to 200 or less and, as the more efficient impulses are transmitted to the ventricle, this usually responds by an increase in rate but a greater regularity in time and force; then suddenly, after 2 or 3 days' treatment, a normal auriculo-ventricular rhythm may be re-established, when the dosage should be reduced gradually and Digitalis substituted if necessary. If the case relapses, Quinidine may be given again and may require to be continued in the minimal beneficial dosage. If after ten days no response is shown, the drug should be discontinued. It should be noted that there is a decided risk in using Quinidine for cases in which fibrillation has continued for some months, because the restoration of the auricular beat may detach clots which form in the stagnant blood in the appendix. The best results are usually obtained in recent cases of fibrillation of thyrotoxic origin and when the Quinidine is given after the heart has been brought fully under the control of Digitalis. Good results have also been recorded in paroxysmal tachycardia. Quinidine is excreted rapidly, and cumulative results from its use are uncommon.

DRUGS ACTING MAINLY ON THE ARTERIES

Vaso-constrictors are drugs which contract the arterioles and thus usually raise blood-pressure.

Adrenalina.—Adrenaline. Epinephrine. *l*-α-3 : 4-Dihydroxyphenyl-β-methyl-amino-ethanol. Prepared from an acid extract of the suprarenal glands of animals or synthetically.



CHARACTERS.—A light-brown or white micro-crystalline powder.

Solubility.—Very slightly in water; neutral or alkaline solutions readily oxidize and turn pink. Combines with acids to form salts which are readily soluble in water.

Dose.—*By injection:*

Metric, 0·1 to 0·5 mg; Imperial, 1/600 to 1/120 gr.

Preparations

1. **Injectio Adrenalinæ.**—Injection of Adrenaline. Adrenaline, 0·1; Tartaric Acid, 0·08; Sodium Metabisulphite, 0·1; Sodium Chloride, 0·8; in Water for Injection, 100.

Dose.—*By subcutaneous injection:*

Metric, 0·12 to 0·5 Mil; Imperial, 2 to 8 min.

2. **Liquor Adrenalinæ Hydrochloridi.**—Solution of Adrenaline Hydrochloride. Adrenaline, 0·1; Chlorbutol, 0·5; Sodium Chloride, 0·9; Dilute Hydrochloric Acid, 0·3; Sodium Metabisulphite, 0·05; Distilled Water, recently boiled and cooled, to 100.

ACTIONS AND USES

Adrenaline is the hormone or chemical mediator which is liberated at all post-ganglionic sympathetic nerve-endings, except those of the sweat glands, when these nerves are stimulated. Since Adrenaline acts even when the post-ganglionic fibres are allowed to degenerate, it must act directly on the adrenergic (sympathetic) receptors in the involuntary muscles and glands. Its action, therefore, is equivalent to stimulation of the sympathetic endings or receptors.

Locally.—If applied to a mucous or raw surface or if injected hypodermically, it stimulates the vaso-constrictor receptors, and local constriction of the arterioles and capillaries results in blanching of the part; this retards the general absorption of the Adrenaline and of any local anæsthetic, e.g. Procaine, which may be injected with it.

Intramuscular or Subcutaneous Injections.—If injected, Adrenaline first increases the rate and force of the cardiac systole by stimulating the accelerator receptors; then, by stimulating the vaso-constrictors, it produces a rapid and high rise in blood-pressure. The increased blood-pressure stimulates the pressor receptors in the aorta and carotid sinus and thus reflexly the vagus centre, hence the cardiac rate usually becomes slower, and as it also depresses the respiratory centre, respiration becomes weaker or irregular. Because Adrenaline is rapidly oxidized by amine-oxidase in the tissues, the rise or blood-pressure lasts only for three to five minutes, and returns to normal or slightly less. The arterial constriction takes place mainly in the skin and the splanchnic area, while the vessels in the voluntary muscles are dilated. The coronary vessels are dilated and the blood-flow to the heart muscle increased but the pulmonary and cerebral vessels are little affected although the cerebral blood-flow may be increased by the rise in blood-pressure. In animals, if the vaso-constrictor myoneural receptors have first been paralysed by Ergotoxine, Adrenaline will cause a fall in blood-pressure, because it will stimulate the vaso-dilator sympathetic endings.

Adrenaline inhibits the movements of the stomach and intestine by stimulating the splanchnic receptors; the pyloric, ileocæcal and internal anal sphincters, which receive motor fibres from the sympathetic, are, however, contracted. By stimulating the sympathetic endings Adrenaline causes **full dilatation of the bronchioles**. Its effects on the bladder and uterus depend on whether the excitor or inhibitory sympathetic receptors are influenced. Usually it relaxes the fundus of the bladder and constricts the sphincter. The uterus in guinea-pigs, rats, and non-pregnant cats is relaxed, whereas in pregnant cats, rabbits and in the human species it is contracted; it may, however, relax the human uterus during parturition. Adrenaline stimulates the glycogenolytic nerves of the liver and by mobilizing the glycogen in the liver, it causes hyperglycæmia and glycosuria. Adrenaline can thus **antagonize hypoglycæmia produced by Insulin**; but, as the liver glycogen may already be depleted in hypoglycæmia, Pituitrin, which antagonizes the action of Insulin in the tissues, may then be necessary. If applied to the conjunctiva, Adrenaline blanches it by constriction of its vessels; it may also widen the palpebral fissure, and produce slight dilatation of the pupil by stimulating the sympathetic receptors which innervate the radiating muscle of the iris, but the pupil still reacts to light. A wide mydriatic response is suggestive of thyrotoxicosis or hyperglycæmia.

Therapeutic Uses.—Applied locally, Adrenaline is commonly used as a **hæmostatic** for capillary hæmorrhage or bleeding from minute vessels; for this purpose the Liquor is applied as a paint or on gauze directly to the bleeding surface. When used in this way the vascular constriction lasts from half an hour to two hours. Adrenaline is of great value in superficial wounds and abrasions, bleeding from the gums, tooth cavities and nose, and is used during operations to stop capillary oozing which obscures the field.

Adrenaline, 1: 2,500 to 1: 1,000, in Olive Oil or Light Liquid Paraffin, along with a volatile oil as an antiseptic, is useful in the form of sprays or local applications to check **nasal inflammation and catarrh** and to relieve hay fever.

Administered by mouth, the Liquor, diluted five or ten times, may serve **to check gastric hæmorrhage** from ulcer, but it is valueless in the intestines as it is decomposed by alkalis. The Liquor, diluted from ten to fifty times with Normal Saline Solution, may also be used as a douche for rectal, vesical, and uterine hæmorrhage.

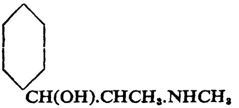
Adrenaline is given by hypodermic injection along with local anæsthetics in order to reduce the circulation in the area and prevent rapid absorption of the anæsthetic drug; in this way Adrenaline **prolongs the local anæsthetic effect** and at the same time diminishes bleeding. The concentration of Adrenaline used in local anæsthetic solutions should be from 0·002 to 0·005 per cent., or 1/2 to 1 min. of the Injection or Liquor in 20 min. of solution; for infiltration anæsthesia, one-tenth of this strength is sufficient. It should be noted that Cocaine potentiates or sensitizes the tissues to Adrenaline and, in nervous or susceptible patients, injections containing both drugs frequently cause alarming, but usually transitory, effects of Adrenaline, such as anxiety, pallor, palpitation, rapid pulse, tremors, etc.

The Injectio Adrenalinæ, given hypodermically, in a dose of 0·2 to 0·3 Mil (3 to 5 min.) is employed **to relieve spasmodic asthma** by dilating the bronchioles; it is speedily effective in acute attacks. Such injections have little effect on blood-pressure in man and may be repeated for severe cases in 15 to 20 minutes, or Ephedrine, which will act in 20 minutes, is given simultaneously by mouth. Hypodermic injections also **relieve the anaphylactic shock** following serum injections and similar reactions after organic arsenicals and spinal anæsthetics. Adrenaline is also used with success in the immediate treatment of the syncopes of Adams-Stokes syndrome, but Ephedrine, having a longer action, is better for maintaining the effect of increasing the conductivity of the Bundle of His.

The use of Adrenaline intravenously in doses of 0·12 to 0·25 Mil (2 to 4 min.) of the Injection, well diluted with Normal Saline and given slowly, is valuable as a **restorative in circulatory collapse** and in cardiac failure, e.g. from drowning. It is given into a vein near the heart and artificial respiration practised to assist its transmission. If this fails or in urgent cases, **intracardiac injection** into the right ventricle of 0·25 Mil (4 min.) of the Injection may resuscitate the heart.

Adrenaline **injections should not be used** in cardiac failure from cyclopropane or chloroform, because these anæsthetics sensitize the heart to Adrenaline and an injection may precipitate fibrillation of the ventricle. They are valueless in remote hæmorrhage.

Isopropyl-*nor*-Adrenaline.—Neo epinine. Isoprenaline. *Dose.*—10 to 30 mg (1/6 to 1/2 gr.) is available in 20 mg (1/3 gr.) tablets for sublingual administration thrice daily in the treatment of asthma. It may also be used by oral inhalation from a glass atomizer, the spray solution containing 1 per cent. *Nor*-adrenaline lacks the N-methyl group of Adrenaline.



Ephedrina.—Ephedrine. $(C_{10}H_{15}ON)_2,H_2O$. The hemihydrate of *l*-α-hydroxy-β-methylaminopropylbenzene. An alkaloid obtained from Chinese plants, Ma Huang, Ephedra sinica, E. equisetina, and other species. N.O. Gnetaceae.

CHARACTERS.—Colourless, prismatic crystals, taste bitter; soluble in water.

Ephedrinæ Hydrochloridum.—Ephedrine Hydrochloride.

CHARACTERS.—Colourless crystals, odourless; taste bitter. *Soluble* 1 in 5 of water, neutral.

Dose.—Metric, 16 to 60 mg; Imperial, 1/4 to 1 gr.

Preparation

Tabellæ Ephedrinæ Hydrochloridi.—30 mg (1/2 gr.) in each.

ACTIONS AND USES

Ephedrine **acts similarly to Adrenaline** because it prevents the rapid destruction of Adrenaline by amine oxidase and thus prolongs the action of the Adrenaline formed naturally at the sympathetic endings. It can be **given by mouth**, producing, when absorbed from the intestine, effects which commence in 20 or 30 minutes and persist for 2 or 3 hours.

The average **rise of blood-pressure** produced by Ephedrine is 28 mm. Mercury; the heart rate may be accelerated at first, but is later slowed by the pressor reflexes from the carotid sinus influencing the vagus centre: the coronary arteries are dilated and conduction through the Bundle of His improved. Ephedrine inhibits the bowel movements and causes a full **dilatation of the bronchioles.** Further, it contracts the uterus, increases the urinary secretion owing to the augmented blood-pressure, and raises the percentage of blood-sugar; the pupil is dilated. Ephedrine **stimulates the cerebrum** and commonly causes insomnia.

Ephedrine has the uses of Adrenaline. Solutions (1 per cent.) of the Hydrochloride are applied as local **hæmostatics** and to decrease hyperæmia and secretions of mucous membranes; similar solutions of Ephedrine base in Light Liquid Paraffin or Olive Oil—with Menthol, Camphor, etc., as antiseptics—are used as sprays in **nasal catarrh, sinusitis** and **hay fever.** Local injections are inadvisable as prolonged vaso-constriction may cause necrosis.

Given by mouth, Ephedrine takes about 20 minutes to relax bronchial spasm in **asthma,** hence it is best preceded by a hypodermic injection of Adrenaline; many moderate cases of allergic type are permanently benefited. Ephedrine is also useful to relieve spasms in emphysema and chronic bronchitis. In **whooping-cough** it reduces the severity of the spasms and the vomiting. Nocturnal incontinence in children and even in adults responds to Ephedrine, which raises the tone of the sphincter and relaxes the detrusor muscle. Ephedrine is also useful in cases of low blood-pressure, in collapse following hæmorrhage or spinal anæsthesia, etc., and to avert syncopal attacks in Adams-Stokes disease and sleep in narcolepsy. As Adrenaline is an antagonist of Curarine, Ephedrine is sometimes given with Neostigmine in myasthenia gravis.

Not uncommonly, *toxic effects* arise from over-dosage: these are headache, giddiness, nausea, sweating, thirst, palpitation, restlessness, muscular tremors, and insomnia.

Amphetamina.—Amphetamine. Benzedrine. Isomyn. β-aminopropylbenzene. $C_6H_5.CH_2.CHNH_2.CH_3$. Prepared by the reduction of the oxime of phenylacetone.

CHARACTERS.—A colourless, volatile liquid, odour slight.

Amphetaminæ Sulphas.—Amphetamine Sulphate. Benzedrine Sulphate.

CHARACTERS.—A white powder, taste bitter followed by numbness. *Solubility.*—1 in 8 of water.

Dose.—Metric, 2·5 to 10 mg; Imperial, 1/24 to 1/6 gr.

ACTIONS AND USES

Amphetamine base, being volatile, is used by inhalation as a vaso-constrictor in hay fever, nasal and pharyngeal catarrhs, and asthma, usually along with Oil of Lavender and Menthol as antiseptics; convenient inhalers are available.

Amphetamine Sulphate delays the oxidation of Adrenaline and acts as a **sympathetic stimulant** peripherally and as a **cerebral stimulant** centrally. Amphetamine Sulphate, given orally, within 1 hour raises the blood-pressure, which attains a maximum in 2 or 3 hours and returns to normal within 24 hours; it has, therefore, been used to treat hypotension if the heart is sound. As it relaxes gastro-intestinal tone, it may be used to relieve spasm of the alimentary tract and to facilitate transmission of a Barium meal during radiological examination. It decreases appetite and Tablets (5 mg) are given thrice daily 1 hour before meals to treat obesity. Like Ephedrine, it induces restlessness and insomnia, associated with increased mental activity, talkativeness, relief of fatigue, and increased physical energy. This cerebral stimulant action is of value to avert sleep in narcolepsy and oculogyric crises in post-encephalitic Parkinsonism, and to alleviate states of mental exhaustion or depression; small doses, gradually increased, reduce the frequency of petit mal attacks; its use in normal persons to relieve fatigue is inadvisable as its cerebral excitant effects vary with individuality.

Methylamphetamina (B.P.C.).—*d*-deoxyephedrine. $C_5H_6.CH_2.CH(NH.CH_3).CH_3$.

Methylamphetaminæ Hydrochloridum (B.P.C.).—Methedrine. Pervitin.
Dose.—*Orally:* **2·5 to 10 mg; Imperial, 1/24 to 1/6 gr.**
By intramuscular or intravenous injection:
Metric, 10 to 30 mg; Imperial, 1/6 to 1/2 gr.

ACTIONS AND USES

Methylamphetamine is a sympathomimetic drug, delaying the oxidation of Adrenaline; it has a prolonged peripheral effect and a more powerful cerebral stimulant action than Amphetamine. It relieves fatigue and increases mental and physical efficiency; it has been used to increase courage and endurance. It is used by injection to raise the blood-pressure in surgical or traumatic shock, spinal anæsthesia and vaso-vagal syncope. Its stimulant action upon the cerebrum is utilised in poisoning from morphine, alcohol or the barbiturates and to alleviate narcolepsy, coma and mental depression.

Pholedrine Sulphate (B.P.C.).—Veritol. β-methylamino-hydroxypropylbenzene sulphate.
Dose.—*Intramuscularly:* **20 to 30 mg. (1/3 to 1/2 gr.).**
Intravenously: **5 to 15 mg. (1/12 to 1/4 gr.).**

ACTIONS AND USES

Pholedrine is a brief peripheral sympathetic stimulant having no cerebral actions. Its effect in raising blood-pressure lasts about half an hour. It is used to restore and maintain blood-pressure during spinal anæsthesia and surgical operations.

Injectio Pituitarii Posterioris.—Injection of Pituitary (Posterior Lobe). Pituitrin. Extractum Pituitarii Liquidum. A sterile aqueous extract of the posterior lobe of the pituitary bodies of oxen or other mammals containing 10 oxytocic Units per Mil. Prepared by extracting the posterior lobes of the pituitary bodies of oxen and other mammals with water acidified with acetic acid, hot enough to coagulate protein and destroy enzymes. The filtrate is assayed, sterilized and sealed in glass ampoules or in phials containing a sufficient proportion of some antiseptic. Phials are labelled with the number of Units per Mil, the date of manufacture, and the date after which it is not intended to be used.

ASSAY.—The International Unit is the activity (oxytocic, antidiuretic or pressor) of 0·5 mg of a Standard, dry, pituitary powder. The comparative activity is determined from the amounts of Extract required to produce (*a*) equivalent contractions of the isolated virgin guinea-pig uterus (oxytocic); (*b*) equivalent times for excretion of urine in rats (antidiuretic); and (*c*) equivalent blood-pressure rises in a spinal cat (pressor).

CHARACTERS.—A colourless fluid; reaction acid, *p*H 3–4.

COMPOSITION.—There are two active principles: *Vasopressin* (Pitressin), which raises blood-pressure and reduces excretion of urine; and *Oxytocin* (Pitocin), which contracts the uterus.

Dose.—*By subcutaneous or intramuscular injection:* 2–5 Units.
Metric, 0·2 to 0·5 Mil; Imperial, 3 to 8 min.

ACTIONS AND USES

The two important principles of Posterior Pituitary Injection produce their chief effects by **direct stimulation of involuntary muscles.** Vasopressin causes constriction of the unstriated muscle of the arterioles, intestine and bronchioles, and it is also antidiuretic; while Oxytocin stimulates uterine contractions and tone.

When injected into an animal, Vasopressin causes a **slower, but more prolonged, rise of blood-pressure** than does Adrenaline, and as it occurs after large doses of Ergotoxine, which paralyses sympathetic receptors, the action is exerted directly on the muscle. The rise of blood-pressure lasts half an hour or longer, and constriction occurs not only in the splanchnic and systemic vessels but also in the pulmonary, cerebral and coronary vessels. In man, a hypodermic or intramuscular injection of Posterior Pituitary Injection does not usually produce any important rise in blood-pressure, but causes, from constriction of both the arterioles and the capillaries, notable pallor of the skin and lips. The **coronary constriction** results in a diminished nutrition and oxygenation of the cardiac muscle; therefore the heart may not only be slowed reflexly by a rise in blood-pressure, but also weakened in force, and the blood-pressure may in consequence fall.

Posterior Pituitary Injection **increases intestinal peristalsis and tone** but does not commonly cause spasmodic contractions; some colic and a desire to defæcate follow. The tone of the bladder and of the bronchioles is increased, and in a lactating animal, by contracting the involuntary muscle of the mammary gland, it produces a profuse flow of preformed milk.

Urinary Secretion.—If injected subcutaneously or intramuscularly, Posterior Pituitary Injection or Vasopressin has an important **antidiuretic action** which in man is most marked after 3 or 4 hours and passes off after about 10 hours. The antidiuretic action is due to an increased reabsorption of water from the convoluted tubules, and the chloride content of the urine increases; even if large quantities of water are drunk after Vasopressin, their excretion is delayed. A slower action is (during 48 hours) gained by using Vasopressin Tannate, suspended in oil.

Metabolism.—Deficiency of Posterior Pituitary leads to obesity, and frequent injections of Pituitrin in animals increase the fat in the liver but decrease the fat in the blood and subcutaneous tissues. Vasopressin can produce hyperglycæmia because it **antagonizes the action of Insulin in increasing the tissue metabolism of sugar**; therefore it is used in hypoglycæmia as an antidote to over-dosage with Insulin, if Adrenaline fails owing to lack of glycogen in the liver.

Uterus.—Posterior Pituitary Injection, owing to Oxytocin, **increases the rhythmic contractions and tone of the uterine muscle**, but the effects in many animals and in man are not marked unless the uterus be pregnant and parturition imminent, because the corpus luteum which persists during pregnancy secretes Progesterone which inhibits the action of Oxytocin. As full term approaches, degeneration of the corpus luteum removes the inhibitory influence and Oxytocin then initiates and maintains the uterine contractions during parturition.

Therapeutic Applications.—These are readily deduced from the pharmacological actions.

Absorption.—Vasopressin can be absorbed from the nasal mucosa, but is destroyed in the intestine. Intranasal sprays of from 0·5 to 5 Mils (7 to 75 min.), or a pledget of lint soaked with 0·5 Mil of the Injection and placed in the nostril, once or twice a day, or snuffs containing Vasopressin 1 per cent. in Lactose, are useful ways of gaining absorption in treating diabetes insipidus.

Hypodermically or Intramuscularly.—Pituitrin is sometimes injected to constrict the peripheral vessels in surgical shock, after severe hæmorrhage and after spinal anæsthetics, but the results are often disappointing. In **acute pneumonia** Pituitrin has been advised if the systolic blood-pressure falls below the pulse rate, and may be repeated until the pressure exceeds the pulse rate or until Digitalis administration improves the circulation. In doses of 0·5 Mil hypodermically, it sometimes affords relief from the initial pain of herpes zoster.

For its stimulant effect on intestinal muscle Pituitrin is useful in **post-operative intestinal atony**, tympanites (meteorism) and in persistent colonic stasis. It may be given along with Physostigmine in these conditions.

In **diabetes insipidus**, where large quantities of dilute urine are excreted, Pituitrin injections relieve the intense thirst, reduce the urinary secretion and increase its concentration. The action lasts from a few hours to a day and some cases show permanent improvement, but usually the injections have to be repeated twice daily to maintain benefit or Posterior Pituitary Injection may be given also intranasally by spray or soaked in a cotton-wool plug.

In diabetes mellitus, its antagonism to Insulin renders a hypodermic injection of Pituitrin (10 Units) of value in hypoglycæmia from over-dosage of Insulin.

Posterior Pituitary Injection in Parturition.—Oxytocin, as a stimulant to the expulsive contractions of the uterus, should be withheld until the second stage is well advanced and the os uteri well dilated. Obstetricians advise that it should not be given until the placenta is expelled and the risk is admitted that its earlier use may cause uterine rupture, asphyxia of the child from compression, or retained placenta from hour-glass contraction. When, however, uterine contractions diminish from fatigue (secondary inertia), Posterior Pituitary Injection in doses of 2 Units, repeated if necessary, is of value; it augments the force and frequency of the rhythmic contractions. In the third stage Posterior Pituitary Injection is sometimes given to assist expulsion of the placenta, but its main use in obstetrics is to ensure contraction of the uterus after the placenta has been expelled and to prevent or check postpartum hæmorrhage.

Injectio Vasopressini.—Injection of Vasopressin. Vasopressin. A sterile aqueous solution containing the pressor and antidiuretic principles from the posterior lobes of the pituitaries of oxen and other animals; supplied in sterilized glass containers. It contains 10 Units (pressor) per Mil.

Dose.—*By subcutaneous or intramuscular injection:*
Metric, 0·5 to 1·5 Mil; Imperial, 8 to 25 min.

ACTIONS AND USES

This is given hypodermically or intramuscularly to treat intestinal atony and meteorism. It is also used, soaked in cotton-wool, for a few minutes intranasally, thrice daily to control diabetes insipidus, or by injection 0·5 Mil (8 min.), which may remain effective for 24 or more hours. Vasopressin Tannate, used as a suspension in oil and injected intramuscularly in dose of 0·5 Mil (8 min.), has, being less soluble, a more prolonged (48 hours) antidiuretic effect and is also less liable to cause nausea and colic. The water-vasopressin test for epilepsy consists in giving 10 fl. oz. of water every 2 hours, an initial dose of 0·5 Mil of Vasopressin Injection, followed by 1 Mil every 4 hours for 40 hours; if no major fit results from the induced water retention, epilepsy is excluded.

Injectio Oxytocini.—Injection of Oxytocin. Oxytocin. A sterile aqueous solution containing the oxytocic principle from the posterior lobes of the pituitaries of oxen and other mammals; supplied in sterilized glass containers. It contains 10 Units (oxytocic) per Mil.

Dose.—*By subcutaneous or intramuscular injection:*
Metric, 0·5 to 1 Mil; Imperial, 8 to 15 min.

ACTIONS AND USES

This has little pressor or antidiuretic action and is used to stimulate uterine contractions, chiefly for the arrest of post-partum hæmorrhage. It may, with due precautions and in small doses (0·2 Mil), be given in secondary uterine inertia.

Vaso-dilators dilate arterioles and lower blood-pressure.

Amylis Nitris.—Amyl Nitrite. A liquid consisting chiefly of the nitrites of *iso*-butyl-carbinol $(CH_3)_2CH.CH_2.CH_2OH$ and *sec*-butyl-carbinol $(C_2H_5)(CH_3)CH.CH_2OH$ and other nitrites of the homologous series. Prepared by the action of Nitrous Acid on Amyl Alcohol distilled between 128° and 132° C.

CHARACTERS.—A yellow, volatile liquid of fragrant odour.

Dose.—*Inhaled:*
Metric, 0·12 to 0·3 Mil; Imperial, 2 to 5 min.

ACTIONS AND USES

Amyl Nitrite is administered by inhalation, 2, 3 or 5 minims being available for use in glass capsules (enveloped in cotton-wool), which, when required, are broken between the fingers and thumb. The vapour enters the circulation through the lungs and produces immediately a sense of fullness and throbbing in the head; visible pulsation of the carotids; flushing of the face, neck and trunk; increased frequency and palpitation of the heart; deeper and more rapid respirations; dilatation of the pupils, and disturbances of vision; giddiness and unsteady gait; restlessness and anxiety of mind. The action, which starts in 10 to 15 seconds, reaches a maximum in 1/2 to 1 minute, and lasts 5 to 10 minutes only, possibly leaving slight headache. Larger doses aggravate all these phenomena, and cause mental confusion, great muscular weakness, coldness of the extremities, and sweats, followed by severe headache; but they rarely produce unconsciousness.

The action of Amyl Nitrite is primarily upon the vascular system, other vital functions being influenced secondarily by the fall in blood-pressure.

The **blood-vessels are dilated** by a direct relaxing action of the Nitrite on the unstriped muscle of the arterioles, so that the peripheral resistance is reduced; therefore the **blood-pressure falls rapidly** with full doses and the pulse becomes dicrotic in type; the veins are also dilated. With doses of 3 min. the maximum fall is about 15 or 20 mm. Mercury. The chief vascular dilatation occurs in the splanchnic area, but the vessels of the limbs and skin also participate; whence arise the flushing of the "blush" area in the face and neck, and the sweating with consequent lowering of temperature.

The reduction of blood-pressure produces anæmia of the cerebrum, which explains the headache, visual dimness and giddiness. The medullary centres are also affected; the medullary vagus control is relaxed and in consequence the **heart becomes greatly accelerated** and the amplitude of its contractions is also increased in an effort to compensate for the reduced blood-pressure. Respiration is accelerated and deepened because the centre receives less blood supply.

Nitrites also relax all other plain muscles in the body by a direct depressant action upon them, but none is so sensitive as the muscle of the arterioles.

Therapeutic Applications.—The chief value of Amyl Nitrite, inorganic nitrites and organic nitrates is to relieve the **pain of angina pectoris,** or angina of effort, because the **dilatation of the coronary arteries** improves the nutrition of the cardiac muscle, and the cardiac pain of hypertensive origin, where the lowered blood-pressure relieves the strain on the overworking left ventricle. Amyl Nitrite, being absorbed quickly, is particularly valuable to give immediate relief from such cardiac pain but its action, and indeed that of other nitrites, is too brief to be more than of temporary value. It should not be used for coronary thrombosis.

In **spasmodic asthma** careful inhalation of Amyl Nitrite, by relaxing the muscle, frequently affords rapid relief, although the dyspnœa may soon return. Spasm of other involuntary muscles, for example the ureter or bile-duct during the passage of a calculus, can be relieved by nitrites. Amyl Nitrite is also effective in arresting the spasms of croup and whooping-cough when these are alarming, but small doses only should be used.

Amyl Nitrite, being volatile, is excreted partly by the breath; the remainder is excreted—like other nitrites and organic nitrates—in the urine as nitrites and nitrates.

Toxic Effects.—Large doses of nitrites and organic nitrates convert oxyhæmoglobin into methæmoglobin, and thus impair the oxygen capacity of the corpuscles; therefore cyanosis and breathlessness are symptoms of poisoning. The blood may become of a chocolate colour and the urine contains acid methæmoglobin.

Octyl Nitrite (B.P.C.).—*Dose.*—By inhalation: 0·2 to 0·4 Mil (3 to 6 min.) has a longer vasodilator action and is less liable to form methæmoglobin than Amyl Nitrite.

Tabellæ Glycerylis Trinitratis.—Trinitrin Tablets. Tablets of Chocolate Basis, 0·3 G (5 gr.) containing 0·5 mg (1/130 gr.) of Glyceryl Trinitrate.
Dose.—Of Glyceryl Trinitrate:
Metric, 0·5 to 1 mg; Imperial, 1/130 to 1/60 gr.

ACTIONS AND USES

Glycerylis Trinitratis **resembles Amyl Nitrite in action** but is somewhat slower. The fall of blood-pressure from doses of 0·5 mg (1/120 gr.) occurs in from 1–2 minutes, reaches a maximum in 5–15 minutes, is similar in degree (20 mm. Mercury), and more prolonged (½ hour or more). It is absorbed best from the sublingual mucosa, hence the Chocolate Tablets are intended to be dissolved in the mouth. It is used for the same class of cases as Amyl Nitrite—angina pectoris, or effort angina, to dilate the coronary arteries, to reduce blood-pressure, and occasionally for asthma. The Tablet, easily taken, acting fairly quickly and for longer time, is preferable to Amyl Nitrite.

Sodii Nitris.—Sodium Nitrite. $NaNO_2$.

CHARACTERS.—A white, crystalline, deliquescent powder. Taste saline. *Solubility.*—1 in 1·5 of water; solution neutral or alkaline.
Dose.—Metric, 30 to 120 Mg; Imperial, 1/2 to 2 gr.

ACTIONS AND USES

Sodium Nitrite lowers blood-pressure **like Amyl Nitrite.** A dose of 2 gr. commences to act in 5 minutes and the maximal effect is reached more slowly (15–30 minutes), is a little greater (about 30 mm. Mercury), and is of longer duration (1–2 hours). Sodium Nitrite causes less headache and flushing than Amyl Nitrite. It is used to lower blood-pressure, and to relieve angina pectoris.

Spiritus Ætheris Nitrosi.—Spirit of Nitrous Ether. Sweet Spirit of Nitre. An alcoholic solution containing not less than 1·25 or more than 2·5% by weight of Ethyl Nitrite $C_2H_5O.NO$, with Acetaldehyde and related substances.

CHARACTERS.—A transparent, yellowish liquid with a peculiar apple-like odour, and sweetish, sharp taste. Slightly acid. *Incompatibles.*—Potassium Iodide, Sodium Salicylate, Antipyrin.
Dose.—Metric, 1 to 4 Mils; Imperial, 15 to 60 min.

ACTIONS AND USES

Spirit of Nitrous Ether is a **diffusible stimulant and carminative** from its alcoholic content. The Ethyl Nitrite by dilating blood-vessels acts as a **diaphoretic** and **diuretic**; it has thus a moderate antipyretic action, and is extensively prescribed for "feverish colds." It also reduces blood-pressure, and accelerates the heart.

Potassium Thiocyanate. KCNS.

CHARACTERS.—Colourless, odourless, soluble crystals, taste saline.
Dose.—*Orally:* **50 to 200 mg (3/4 to 3 gr.).**

ACTIONS AND USES

Potassium Thiocyanate relaxes smooth muscle and has been used in treating hypertension. Initial doses of 0·1 G (1½ gr.) in Chloroform Water are given thrice daily after food and the dose regulated to give a serum-thiocyanate level between 4 and 8 mg per 100 Mils; this dose may be about 0·2 G (3 gr.) thrice weekly. In quiescent cases, there are significant reductions in systolic and diastolic pressures and a symptomatic relief, but less effects are obtained in active cases and in renal hypertension. Malaise, nausea and rashes may arise as side effects.

Tetræthyl-Ammonium Bromide.—(T.E.A.B.).

Dose.—*Intravenously:* **0·1 to 0·5 G (3 to 8 gr.)** in 10% solution.
Intramuscularly: **up to 20 mg per Kg** body weight.

ACTIONS AND USES

Tetraethyl-ammonium bromide acts by blocking sympathetic and parasympathetic ganglia. It gives symptomatic relief in hypertensive, congestive, cardiac failure, but the fall in pressure lasts only some 15 to 60 minutes. Side effects—dry mouth, and skin, pupillary dilatation, and constipation—have been recorded.

Priscol.—2-benzyl-4 : 5-imidazoline hydrochloride. *Dose.—Orally:* 25 to 50 mg; *by injection:* 5 to 20 mg. Available as tablets of 25 mg and ampoules of 10 mg in 1 Mil. This is a sympatholytic drug, antagonizing Adrenaline. It is used as a peripheral vaso-dilator in Raynaud's disease, thrombophlebitis and similar conditions of vascular spasm.

Dibenamine.—Dibenzyl-β-chloroethylamine, acts similarly.

DRUGS INFLUENCING THE RESPIRATORY SYSTEM

The **respiratory centre** in the medulla is stimulated reflexly by sensory impulses, e.g. inhalation of Ammonia, and directly by Carbon Dioxide, and the analeptics, Nikethamide, Leptazol, Picrotoxin, Strychnine, and Caffeine; it is depressed directly by

Morphine, Codeine, Diamorphine, General Anæsthetics and Hypnotics. The related **cough centre** is stimulated by Strychnine, and depressed by Morphine, Codeine and Diamorphine. The **bronchioles** can be dilated by parasympathetic depressants, e.g. Atropine; by sympathetic stimulants, e.g. Adrenaline, Ephedrine and Amphetamine; by ganglionic depressants, e.g. Lobelia; or by muscular depressants, e.g. Nitrites. **Expectorants** increase and liquefy the bronchial secretion; they act either (1) *reflexly*, by irritation of the stomach, e.g. Ipecacuanha, Ammonium Bicarbonate, Squill, Senega, Quillaia; (2) *centrally*, by stimulating the medullary vomiting centre, e.g. Apomorphine; (3) *peripherally*, by stimulating the secretory vagal endings, e.g. Pilocarpine (not used owing to its other actions); or (4) *by direct stimulation of the glands*, during their excretion, e.g. Potassium Iodide and Volatile Oils. Bronchial secretion can be prevented by parasympathetic depressants, e.g. Atropine. Respiratory Antiseptics are either Volatile Oils, e.g. Abietis, Eucalyptus, or phenols, e.g. Creosote, Guaiacol, which are inhaled as vapours or given by mouth as they are partly excreted by the bronchial mucous membrane; their antiseptic value is small, but they promote a more fluid secretion.

Ipecacuanha.—Ipecacuanha Root. The dried root of Cephaëlis Ipecacuanha. N.O. Rubiaceæ.

CHARACTERS.—Tortuous, annulated, brown roots; taste bitter.

COMPOSITION.—Ipecacuanha contains not less than 2% of alkaloids, *emetine*, $C_{28}H_{37}(CH_3)N_2O_4$; *cephaëline*, $C_{28}H_{38}N_2O_4$, more powerfully emetic than emetine, about 1%; and *psychotrine*; a glycosidal acid, *ipecacuanhic acid*, $C_{14}H_{18}O_7$; and starch.

Ipecacuanha Præparata.—Prepared or powdered Ipecacuanha. Finely powdered Ipecacuanha Root diluted if necessary with Lactose to contain 2% of total alkaloids calculated as Emetine.

Dose.—*Expectorant:*
Metric, 30 to 120 mg; Imperial, 1/2 to 2 gr.
Emetic:
Metric, 1 to 2 G; Imperial, 15 to 30 gr.

Preparations

1. **Extractum Ipecacuanhæ Liquidum.**—Alcoholic 80%. *Standardized* to contain 2% of alkaloids.

Dose.—*Expectorant:*
Metric, 0·03 to 0·12 Mil; Imperial, 1/2 to 2 min.
Emetic:
Metric, 0·6 to 2 Mils; Imperial, 10 to 30 min.

2. **Tinctura Ipecacuanhæ.**—Vinum Ipecacuanhæ. Liquid Extract 5% with Dilute Acetic Acid, Alcohol, Glycerin and Water.

Dose.—*Expectorant:*
Metric, 0·6 to 2 Mils; Imperial, 10 to 30 min.
Emetic:
Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

3. **Pulvis Ipecacuanhæ et Opii.**—Pulvis Ipecacuanhæ Compositus. Dover's Powder. Prepared Ipecacuanha and Opium each 10% in Lactose. A light fawn-coloured powder.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

4. **Tabellæ Ipecacuanhæ et Opii.**—0·3 G (5 gr.) in each.
5. **Tabellæ Acidi Acetylsalicylici cum Ipecacuanha et Opio.**—0·162 G (2½ gr.) each of Acetylsalicylic Acid and Dover's Powder.
6. **Troschisci Morphinæ et Ipecacuanhæ.**—Each Lozenge contains 2 mg (1/32 gr.) Morphine Hydrochloride and 6 mg (1/10 gr.) Ipecacuanha.

ACTIONS AND USES

Externally.—Ipecacuanha is irritant to mucous membranes. In the mouth it produces reflex salivation; in the pharynx, larynx and bronchi the irritation leads to coughing, with increased flow of mucus. In the form of the Lozenge it is used to relieve dry pharyngeal and laryngeal cough.

Internally.—In the *stomach*, Ipecacuanha in very small doses is a **gastric stimulant**, increasing the local circulation and secretions. It is occasionally prescribed as an adjuvant in bitter stomachic mixtures.

In large doses Ipecacuanha acts as a **reflex emetic** and produces vomiting with the usual symptoms of nausea, e.g. salivation, bronchial secretion, about 20 to 30 minutes after its administration. The emesis is due to reflex stimulation of the medullary vomiting centre by the irritant action of Emetine and Cephaëline on the sensory vagal endings in the stomach, because emesis follows more rapidly after oral doses than after hypodermic injections, which produce vomiting only after sufficient Emetine has been excreted into the stomach. Moderate depression and muscular weakness follow the act of vomiting, the pulse is weaker but more rapid, the blood-pressure falls somewhat, and respiration is quicker.

Ipecacuanha is suitable as an emetic only in cases where the necessity for evacuation of the stomach is not urgent. It is too slow for use, as a rule, in poisoning, but may be employed in young children to empty the stomach of unwholesome matter. It is useful also in the bronchitis of children, in croup and in whooping-cough, to expel mucus from the air-passages by the strong expiration following the act of vomiting. The Tincture is the most suitable preparation.

Ipecacuanha, in sub-emetic doses, is a **reflex expectorant,** increasing and liquefying the bronchial secretion. This is a reflex effect of its slow nauseating action and, because of its slow action, Ipecacuanha is a more efficient and lasting expectorant than Ammonium Bicarbonate or Apomorphine. This more fluid bronchial secretion is more easily removed, therefore cough is rendered more effective and less exhausting. Ipecacuanha is extensively given in acute and chronic bronchitis, whooping-cough, croup, and in other bronchial affections where the sputum is tough and scanty.

Ipecacuanha is a useful **reflex diaphoretic**; this effect is again due to the gastric irritation and is developed more strongly in combination with Opium, e.g. as Dover's Powder, in which the Opium serves to prevent an emetic action and induces sleep. The perspiration is not profuse, but is sufficient to exert an antipyretic effect in simple chills and bronchial catarrhs.

In the *intestine* Ipecacuanha in large doses is an irritant and will cause diarrhœa. Large doses of Ipecacuanha—2 to 6 G (30 to 90 gr.)—along with Opium to prevent emesis, were found to check hæmorrhage and diarrhœa in **amœbic dysentery**; this curative action is due to Emetine.

Emetinæ Hydrochloridum.—Emetine Hydrochloride, $C_{28}H_{37}(CH_3)N_2O_4$, $2HCl,7H_2O$. Obtained from Ipecacuanha or by methylation of cephaëline.

CHARACTERS.—Colourless crystals, odourless, taste bitter, becomes yellow if exposed to light. *Soluble* in water.

Dose.—*Daily, by subcutaneous or intramuscular injection:*

Metric, 30 to 60 mg; Imperial, 1/2 to 1 gr.

Preparations

1. **Injectio Emetinæ Hydrochloridi.**—A sterile solution in Water for Injection. Contains 60 mg (1 gr.) in 1 Mil (15 min.).
2. **Emetinæ et Bismuthi Iodidum.**—Emetine Bismuth Iodide. A complex double iodide containing from 25 to 29% of Emetine and 18 to 22% of Bismuth.

CHARACTERS.—A reddish powder, odourless; taste bitter, acrid. Insoluble in water; *soluble* in alkaline solutions.

Dose.—*Daily:*

Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

ACTIONS AND USES

When Emetine Hydrochloride is injected, it is excreted by the stomach, intestine, and, largely, through the colon. Although not highly toxic to the amœba of dysentery *in vitro* it is toxic in dilutions of 1: 50,000 *in vivo.*

Emetine is used to treat acute **amœbic dysentery.** Doses of the

Injection, 1/2 Mil twice or 1 Mil once daily, are given intramuscularly, as it is somewhat irritant subcutaneously, for 7 to 10 days. This treatment rids the intestine of the amœbæ within a few days, checks ulceration and hæmorrhage in the bowel, and diminishes the risk of hepatitis and liver abscess. If amœbæ be still present after a course, a week's rest must be given before repetition, because Emetine is itself an intestinal irritant and can cause enteritis; it also tends to produce myocardial weakness, and this precludes its intravenous use. For liver abscess Emetine should be given intramuscularly, and, in addition, the abscess should be aspirated and 1 to 2 oz. of a 0·1 per cent. Emetine solution injected. Treatment orally with Acetarsol or Carbarsone (*see* p. 108) during the intervals of Emetine administration is very advantageous in promoting cure. Emetine has also proved useful in pulmonary amœbiasis, bilharziasis (schistosomiasis) and, by local injection (20 min. of 5 per cent.), in dermal leishmaniasis (Oriental sore). Emetine Periodide (1–2 gr.) thrice daily by mouth gives good results in children infected with bilharzia, thus avoiding intravenous injections of Antimony; it rarely causes sickness, as it is insoluble in the stomach, and is useful for dysenteric carriers.

Emetine Bismuth Iodide in dose of 60 mg (1 gr.), by mouth thrice daily for 12 days, should pass through the stomach undissolved, but, as it may cause vomiting, it is best given as enteric-coated pills or in gelatin capsules; it is more effective in removing the encysted forms and is therefore more valuable for chronic dysenteric cases and carriers.

Other drugs used in amœbic dysentery are Acetarsol (p. 108), Carbarsone (p. 108), Chiniofon or Yatren (p. 361).

Berberine Sulphate in 2% solution (Orisol) injected weekly in amounts of 2 to 3 c.c. hypodermically around oriental sore is usually curative after three injections.

Senega.—Senega Root. The dried root of Polygala Senega. N.O. Polygaleæ.

CHARACTERS.—Brown, slender, curved roots, with a keel and a knotty crown.

COMPOSITION.—Two glycosidal saponins, *senegin*, $C_{18}H_{28}O_{10}$, and *polygalic acid.* Saponins are decomposed by acids in presence of water into sugar and sapogenins; their watery solutions froth if shaken and, by lowering surface tension, emulsify oils and tars.

Preparations

1. **Extractum Senegæ Liquidum.**—Senega percolated with Alcohol 60% and made faintly alkaline with Ammonia.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

2. **Tinctura Senegæ.**—Liquid Extract 20% in Alcohol 60%.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
3. **Infusum Senegæ Concentratum.**—Concentrated Infusion. Senega 40% percolated with Alcohol 25% and made faintly alkaline with Ammonia.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.
4. **Infusum Senegæ.**—Concentrated Infusion 12·5% in Distilled Water; use within 12 hours.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

ACTIONS AND USES

Externally.—Tincture of Senega emulsifies oils and tars.

Internally.—Senega is moderately irritant to the stomach and intestines; large doses cause nausea and diarrhœa.

Senega is a **reflex expectorant,** increasing and liquefying the bronchial secretion, because of its irritant action on the stomach. It is somewhat less nauseating than Ipecacuanha, but has no other advantages. Senega is used in acute and chronic bronchitis, in bronchiectasis, and in other conditions where the sputum is tenacious.

Actions of Saponins.—When added to blood-corpuscle suspensions, saponins produce hæmolysis by uniting with the lecithin of the corpuscular wall and rendering this permeable; if injected into animals, saponins cause locally a sterile inflammation with severe and lasting pain, followed by gastro-intestinal inflammation with submucous hæmorrhages; punctiform hæmorrhages also occur on the surfaces of the heart, lungs, abdominal organs and brain.

Quillaia.—Quillaia Bark. The dried inner part of the bark of Quillaja Saponaria. N.O. Rosaceæ.

CHARACTERS.—Flat pieces; outer surface brownish-white, inner surface yellowish-white. Fracture splintery, showing glistening crystals of calcium oxalate; taste astringent and acrid.

COMPOSITION.—Two glycosidal saponins, *quillaia-sapotoxin* (irritant and acrid), and *quillaiac acid.*

Preparation

Extractum Quillaiæ Liquidum.—1 in 1 of Alcohol (45%).

ACTIONS AND USES

Quillaia emulsifies oils, resins, and tar and is used in Liquor Picis Carbonis and the Extract in Emulsions of Chloroform and Peppermint. It was formerly used as a **reflex expectorant.**

Balsamum Tolutanum.—Balsam of Tolu is obtained by incising the trunk of Myroxylon Toluifera. N.O. Leguminosæ.

CHARACTERS.—A soft, tenacious, brown solid, becoming hard and showing crystals of cinnamic acid. Odour fragrant; taste aromatic. *Solubility.*—In alcohol 90% with acid reaction.

COMPOSITION.—Free *cinnamic acid* 12%, and *benzoic acid* 8%; *benzyl benzoate*; *benzyl cinnamate*; and a resin, yielding *benzoic acid* and *tolu-resinotannol.*

Preparations

1. **Syrupus Tolutanus.**—Tolu Balsam, 2·5% with Sucrose and Distilled Water.
Dose.—Metric, 2 to 8 Mils; Imperial, 30 to 120 min.
2. **Tinctura Tolutana.**—Tolu Balsam, 10% in Alcohol 90%; by solution.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Balsam of Tolu is antiseptic, parasiticidal and stimulant on the skin, but Balsam of Peru is preferred for external use (p. 429). Syrup of Tolu is a **mild reflex expectorant**, and is used for its pleasant flavour in cough mixtures for bronchitis and the Tincture in lozenges for sore throat.

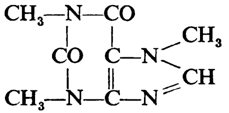
Balsam of Peru (p. 429), Benzoinum (p. 368), and Volatile Oils have also slight expectorant properties.

DRUGS INFLUENCING THE NERVOUS SYSTEM

These drugs may be conveniently grouped into:

(1) *Stimulants*, e.g. Caffeine, Strychnine, Ephedrine, Amphetamine, Cocaine; (2) *Depressants*, including general anæsthetics, anodyne narcotics, e.g. Opium, and organic hypnotics, e.g. Chloral Hydrate, Barbiturates; (3) *Parasympathetic Stimulants*, e.g. Physostigmine; (4) *Parasympathetic Depressants*, e.g. Atropine; (5) *Local Anæsthetics*, e.g. Cocaine.

Caffeina.—Caffeine. Theine. 1 : 3 : 7-trimethylxanthine.



An alkaloid obtained from the dried leaves of Camellia sinensis, the tea plant. N.O. Ternstrœmiaceæ, or other plants.

CHARACTERS.—Colourless, silky, crystals. *Solubility.*—1 in 80 of water; solution faintly bitter; neutral. *Test.*—Caffeine evaporated with a crystal of $KClO_3$ and HCl to dryness leaves a reddish residue which becomes purple with NH_4OH.

Tea contains about 3·3% of Caffeine, with tannic acid, volatile oil, etc.; Coffee, about 1·3%, with volatile oil, sugar, tannic acid, etc.; Maté, 1·2%; Guarana, 4·5%.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparations

1. **Caffeina et Sodii Benzoas.**—Caffeine and Sodium Benzoate. A mixture of equal parts of anhydrous Caffeine with Sodium Benzoate. CHARACTERS.—A white powder; odourless, taste slightly bitter. *Solubility.*—1 in 1 of warm water, and in 4 of cold water.

Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

By subcutaneous injection:

Metric, 0·12 to 0·3 G; Imperial, 2 to 5 gr.

2. **Injectio Caffeinæ et Sodii Benzoatis.**—A sterile solution in Water for Injection, 0·25 G (3¾ gr.) in 1 Mil (15 min.).

ACTIONS AND USES

Caffeine, being bitter, acts as a sialagogue. Large doses sometimes cause indigestion. A cup of tea contains from 1 to 2 gr. and a cup of coffee from 1½ to 3 gr. of Caffeine.

Caffeine is absorbed unchanged, and acts chiefly as a **stimulant to the central nervous system.** After a moderate dose, there follows stimulation of the cerebral areas associated with the intellectual functions of reason, judgment, will and self-control; association of ideas is also facilitated, but conversion of thought into action may be retarded because the more acute judgment interferes. Perceptions also are rendered more acute, so that pain is felt more keenly and touch becomes more discriminating. Caffeine also **stimulates the motor area** of the cerebrum, producing increased speed and accuracy of movements in man; and, by central action, postpones or **relieves both mental and muscular fatigue.** It also augments "conditioned reflexes." Caffeine **stimulates the medullary centres**; thus respiration is accelerated but may be shallower owing to reduction in the CO_2 tension; the pulse may be sometimes slowed from vagal stimulation but the pulse and blood-pressure may be variable owing to the peripheral effects of Caffeine.

For its effects on the cerebrum, Caffeine is familiarly used in tea and coffee to relieve mental and physical fatigue; in the form of powders along with Aspirin and Phenacetin, it may be used to relieve nervous headache, hemicrania, migraine and neuralgia. As a medullary stimulant, its chief value is as a **stimulant of the respiratory centre** in poisoning from Alcohol, Morphine, organic narcotics, or carbon monoxide; it is readily available in the form of strong coffee but, in urgent cases, Caffeine and Sodium Benzoate may be injected hypodermically but it has not the powerful effects of Picrotoxin or Nikethamide.

In animals, Caffeine **accelerates the cardiac rhythm** by shortening diastole through stimulation of the rhythmogenic area, and augments the strength of the systole by stimulating the cardiac muscle. In man, the effects of Caffeine on the circulation are very variable. It may, by stimulating the vagus and vaso-motor centres, cause some slowing of the heart but a small rise in blood-pressure. This central action on the medulla is, however, usually overcome by its peripheral actions in stimulating the rhythmogenic area and in directly relaxing the muscle of the arterioles. Therefore, it generally accelerates the cardiac rhythm slightly and, by dilatation of the peripheral vessels, lowers blood-pressure to a small degree, which together would account for its increasing the peripheral blood-flow. It dilates the coronary vessels and thus improves the cardiac nutrition. Caffeine is not useful as a cardiac stimulant, although, for its diuretic effect, it is given along with Digitalis. It is sometimes advised in angina pectoris and in hyperpiesia but the preparations of Theobromine and Theophylline are better and they do not cause insomnia.

Caffeine is a **diuretic**, increasing the amount both of the water and of the solids of the urine. Its action is due to dilatation of the renal vessels, to the accelerated blood-flow through them, and to the increased number of glomeruli in operation which increases the filtration. There is little support for the views that it increases the permeability of the glomeruli, decreases reabsorption from the tubules, or diminishes the imbibing power of the tissue colloids.

Caffeine is not irritant to the kidney and may be used in nephritis. Caffeine is a valuable diuretic in cardiac disease, where it is used to prevent or remove slight degrees of œdema and is often prescribed with Digitalis. In hepatic or renal œdema Caffeine is not so reliable, and is only palliative. Caffeine is less efficient as a diuretic than the preparations of Theobromine or Theophylline (*see* p. 370).

Caffeine is to a small extent excreted in the urine unchanged; most is decomposed through the lower methyl-xanthines into xanthine and some into urea.

Large doses cause headache, insomnia, restlessness from motor stimulation, disturbances of the special senses and may produce increased activity of the reflexes and cardiac arrhythmia. Striated muscles immersed in a weak solution of Caffeine contract to weaker stimuli and against greater resistance, because the tissue oxidation is increased, and the onset of fatigue is delayed; but, with strong solutions, the lactic acid formed converts the myosinogen into myosin and the muscle becomes opaque and stiff (rigor mortis).

Nux Vomica.—Nux Vomica. The dried ripe seeds of Strychnos Nux-vomica. N.O. Loganiaceæ.

CHARACTERS.—Disc-shaped, greyish, large, satiny-haired seeds, margin rounded with raised line to the central hilum; taste extremely bitter. Content not less than 1·2% Strychnine.

COMPOSITION.—Nux Vomica contains two alkaloids—*strychnine*, and *brucine* $C_{23}H_{26}N_2O_4$, combined with *caffeotannic acid*; also a glycoside, *loganin*.

Nux Vomica Præparata.—Prepared or powdered Nux Vomica. Nux Vomica in fine powder adjusted by addition of Lactose to contain 1·2% of Strychnine; 250 mg (4 gr.) contains 3 mg (1/20 gr.) Strychnine.

Dose.—Metric, 60 to 250 mg; Imperial, 1 to 4 gr.

Preparations

1. **Extractum Nucis Vomicæ Liquidum.**—Alcoholic; by percolation process. *Standardized* to contain 1·5% of Strychnine; 0·2 Mil (3 min.) contains 3 mg (1/20 gr.) Strychnine.
Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.
2. **Extractum Nucis Vomicæ Siccum.**—Made by percolation with Alcohol 70%, evaporating and adding Calcium Phosphate. *Standardized* to contain 5% of Strychnine; 60 mg. (1 gr.) contains 3 mg (1/20 gr.) Strychnine.
Dose.—Metric, 15 to 60 mg; Imperial, 1/4 to 1 gr.
3. **Tinctura Nucis Vomicæ.**—Liquid Extract, 8·34% with Alcohol 90% and Water. *Standardized* to contain 0·125% of Strychnine; 2 Mils (30 min.) contains 2·5 mg (1/30 gr.) Strychnine.
Dose.—Metric, 0·6 to 2 Mils; Imperial, 10 to 30 min.

Strychninæ Hydrochloridum.—Strychnine Hydrochloride. $C_{21}H_{22}N_2O_2$, $HCl,2H_2O$. The hydrochloride of the alkaloid Strychnine obtained from Nux Vomica seeds.

CHARACTERS.—Small, colourless, prismatic crystals. *Solubility.*—1 in 40 of water, solution neutral; taste intensely bitter. *Test.*—A small amount in sulphuric acid gives, on adding a crystal of potassium bichromate, an intense violet, then red and yellow colours.

Dose.—*Orally:*
Metric, 2 to 8 mg; Imperial, 1/30 to 1/8 gr.
By subcutaneous injection:
Metric, 2 to 4 mg; Imperial, 1/30 to 1/16 gr.

Preparations

1. **Injectio Strychninæ Hydrochloridi.**—A sterile solution in Water for Injection. Contains 4 mg (1/16 gr.) in 1 Mil (15 min.).
2. **Liquor Strychninæ Hydrochloridi.**—Strychnine Hydrochloride 1% in Alcohol 90% and Distilled Water. 0·8 Mil (12 min.) contains 8 mg (1/9 gr.) Strychnine HCl.
Dose.—Metric, 0·2 to 0·8 Mil; Imperial, 3 to 12 min.

ACTIONS AND USES

Internally.—Nux Vomica and Strychnine have an intensely bitter taste, and thus stimulate salivation, appetite and gastric secretion in atonic dyspepsia (*see* p. 158).

Strychnine **improves the peristalsis** and tone of the intestine by increasing the reflex excitability of Auerbach's plexus but it is not itself a purgative. Prepared Nux Vomica, or the Dry Extract, which are more slowly absorbed than Strychnine, have a more prolonged intestinal effect. They are given usually in pills along with an anthraquinone purgative to relieve chronic constipation due to atony of the colon.

Strychnine is absorbed rapidly from the intestine and in *medicinal doses* Strychnine **increases the reflex excitability of the spinal cord**, so that the responses to peripheral reflexes, e.g. the knee-jerk, are augmented. In general, the threshold for sensory stimuli is lowered, the person becomes more responsive to external stimuli, and the tone of the voluntary muscles is slightly increased.

On the cerebrum, the effects of Strychnine are of small therapeutic importance. Strychnine has no action on the intellect, but it increases to a small degree the sensitivity of the **special senses**; touch is more delicate, taste and smell more discriminative, hearing more acute and the visual field increased, especially for the perception of blue rays. This last effect may be a local one on the retinal nerve cells as it occurs from instillation into one eye. In animals, the motor area becomes more sensitive to stimuli, and, in man, a slight increase in muscular energy and delay in fatigue has been determined. The medullary centre of respiration is also stimulated and breathing rendered more rapid and usually deeper. For these several reasons, Strychnine is often described as a nervine tonic but its only important effects in therapeutic doses are the increased reflex excitability and the respiratory stimulation.

Repeated full doses may produce, by cumulation, twitchings of the limb muscles, stiffness in the neck and face, a constricted feeling in the neck or chest with some dysphagia, and a feeling of apprehension; reflex action is much augmented and the person is startled by slight causes.

Poisonous doses produce violent **tetanic convulsions** in which the flexors and extensors both participate; but as the latter are usually the more powerful muscles, the limbs are rigidly extended, the head thrown back and the trunk arched (opisthotonos). In man the angles of the mouth are drawn back (risus sardonicus), and the face cyanosed owing to the arrest of respiration. The muscles are at first rigid, as in tetanus; but, in about thirty seconds, tremors commence, and, after some spasmodic contractions, the muscles relax completely from fatigue of their motor cells in the spinal cord. Reflex irritability, however, rapidly increases again until, in response to some stimulus, another convulsion ensues. The intellect and consciousness remain unaffected. Death takes place from asphyxia due to failure of the respiratory reflex to recover after a convulsion.

Strychnine convulsions arise from the spinal cord and are produced only in response to an afferent impulse. Briefly, Strychnine **diminishes the resistance of the sensory tracts in the cord to the conduction and abolishes the co-ordination of afferent stimuli**; thus a stimulus which is normally confined to one path spreads under Strychnine unresisted through the cord to stimulate all motor neurons. Further, a stimulus, which normally is co-ordinated to cause a flexor contraction associated with inhibition of the antagonist extensor muscle, produces contraction of both flexor and extensor owing to the abolition of reciprocal innervation.

The **medullary centres are stimulated** in proportion to their dependence on sensory impulses. The **respiratory centre**, which receives afferent impulses through the vagus nerve, is stimulated and breathing becomes more rapid and usually deeper; the **cough centre** is also rendered more easily excitable if there is mucus in the bronchioles.

On the **heart,** Strychnine has no direct action, and it is not a cardiac stimulant. When injected in man, it usually slows the heart by stimulating the vagus centre, and does not increase the force of either the auricles or ventricles and, although it stimulates the vaso-motor centre, it rarely raises the blood-pressure much in therapeutic dosage. During convulsions the blood-pressure rises enormously, because of the muscular tetanus.

Motor nerves and muscles are not affected by Strychnine in man. Strychnine augments the tone and rhythmic contractions of involuntary muscles, probably by facilitating local reflexes, as is seen in the intestine, uterus, bladder, etc.

Strychnine is excreted in the urine rather slowly, therefore toxic symptoms may occur from cumulation.

Therapeutic Uses.—Strychnine has been employed in paralysis, unaccompanied by rigidity or spasm, from disease of the cord, but is rarely of real service in cases of organic or inflammatory disease. It may be useful in "functional" paralysis; in diphtheritic paralysis; in nocturnal incontinence; and in peripheral paralyses due to lead, tobacco or alcohol. In sensory paralysis Strychnine is generally useless, but it may improve the toxic amblyopia of tobacco or alcohol, and decrease some forms of deafness.

As a stimulant to the respiratory centre and its related cough centre, Strychnine is sometimes of value in bronchitis and pneumonia **to increase the vigour of cough and the respiratory movements**. It is advantageously combined with expectorants, which, by liquefying the secretion, aid its removal. In pneumonia it is advisable to withhold Strychnine before the crisis unless respiratory failure supervenes, when a hypodermic injection should be given. In **respiratory failure** during anæsthesia, Morphine or other medullary poisoning, Strychnine, hypodermically, is often given to maintain respiration over the critical period, but it is less powerful than other analeptics.

Brucine acts like Strychnine, but is very much weaker.

Analeptics (from *analeptikos*, recovery) may be defined as restoratives which stimulate powerfully the respiratory centre and, to a lesser degree, the vaso-motor centre. They will include Strychnine and Caffeine, already discussed, and Nikethamide, Leptazol, Picrotoxin and Lobeline.

Nikethamidum.—Nikethamide. Coramine. Anacardone. Pyridine-β-carboxylic diethylamide. $C_5H_4N.CO.N(C_2H_5)_2$.

CHARACTERS.—A yellowish, oily liquid or crystalline solid; taste slightly bitter; miscible with water.

Dose.—*Orally:*

Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

By subcutaneous, intramuscular or intravenous injection:

Metric, 0·25 to 1 G; Imperial, 4 to 15 gr.

Preparation

Injectio Nikethamidi.—A 25% solution in Water for Injection. Contains 1 G (15 gr.) in 4 Mils (60 min.).

Dose.—*By subcutaneous, intramuscular or intravenous injection:*

Metric, 1 to 4 Mils; Imperial, 15 to 60 min.

ACTIONS AND USES

Nikethamide is a direct **stimulant of the respiratory and vasomotor centres** in the medulla. When given orally its effects are not very powerful, but when injected subcutaneously or intramuscularly it causes more rapid and deeper respirations, the action being less powerful but lasting longer than that of Leptazol. Intravenous administration arouses deep gasping respiration for a short time and is usually reserved for respiratory failure from poisoning.

A rise in blood-pressure may occur from vaso-constriction, but it is usually slight in man as compared with animals. It is not a direct cardiac stimulant and has little effect on the coronary circulation.

Nikethamide is used successfully in the treatment of respiratory failure during pulmonary diseases, and following poisoning from morphine, organic hypnotics—particularly the barbiturates—general anæsthetics and carbon monoxide. The injections may be repeated at two- or four-hourly intervals if necessary. It is also recommended for acute heart failure and for vaso-motor collapse from hæmorrhage or traumatic shock, but in such cases Methylamphetamine is a more certain restorative and may also be given.

Large doses of Nikethamide cause tremors and convulsions; it was formerly used in the convulsive treatment of schizophrenia.

Leptazolum.—Leptazol. Cardiazol. Metrazol. Pentamethylenetetrazol. $(CH_2)_5.CN_4$.

CHARACTERS.—Colourless crystals or powder, taste pungent, bitter; readily soluble in water.

Dose.—*Orally:* **Metric, 50 to 100 mg; Imperial, 3/4 to 1½ gr.**

Preparation

Injectio Leptazoli.—A 10% solution with 0·25% Sodium Phosphate in Water for Injection.

Dose.—*By subcutaneous injection:*

Metric, 0·5 to 1 Mil; Imperial, 8 to 15 min.

ACTIONS AND USES

Leptazol **stimulates the respiratory and vaso-motor centres** directly; its action is greater but rather less prolonged than that of Nikethamide. It has more activity in raising the blood-pressure and is stated to dilate the coronary arteries, thus it may indirectly improve the heart. Leptazol is usually administered by subcutaneous injection to restore respiration in pneumonia, drowning, and poisoning from alcohol, anæsthetics, morphine, barbiturates and carbon monoxide; it may be repeated at hourly intervals.

Leptazol is also employed in circulatory collapse where it produces a gradual rise in pressure, but more advantageous is the use of alternate doses of Leptazol and Methylamphetamine.

Leptazol Injection was formerly used in doses of 2 Mils increasing to 12 Mils as a convulsant in treating schizophrenia, but electrical convulsive therapy is less unpleasant.

Picrotoxinum.—Picrotoxin. Cocculin. $C_{30}H_{34}O_{13}$. A glycoside from the seed of Anamirta paniculata. N.O. Menispermaceæ.

CHARACTERS.—Flexible, prismatic crystals or powder. *Solubility.*—1 in 334 of water.
Dose.—Metric, 0·6 to 3 mg; Imperial, 1/100 to 1/20 gr.

Preparation

Injectio Picrotoxini.—A sterile solution in Water for Injection. Contains 3 mg (1/20 gr.) in 1 Mil (15 min.).
Dose.—*Of Picrotoxin by intramuscular or intravenous injection:*
Metric, 0·6 to 3 mg; Imperial, 1/100 to 1/20 gr.

ACTIONS AND USES

Picrotoxin is a powerful stimulant of the respiratory centre; to a less extent, it stimulates the vaso-motor and other medullary centres. In overdose the stimulation of the medulla and midbrain causes clonic and tonic convulsions preceded by a period of muscular twitchings.

Picrotoxin has a slower but more prolonged action than Leptazol; it is usually given either intramuscularly or intravenously. It disappears from the blood within two hours, hence small doses at intervals of 15 to 30 minutes have been found most effective.

Picrotoxin is used to treat respiratory failure, but it is of special value in poisoning by the barbiturates and by Morphine.

Lobeline Hydrochloride (B.P.C.).—*Dose.*—By intramuscular injection: 3 to 9 mg (1/20 to 3/20 gr.). Lobeline stimulates the respiratory centre, and also the vagus centre, by increasing the sensitiveness of the carotid sinus reflexes. It accelerates respiration, but slows the heart and lowers blood-pressure, like nicotine. It has been used in respiratory failure during anæsthesia, and from narcotic and coal-gas poisoning, but it is unreliable and brief in its effects; it is unsafe in cardiac disease unless given with Atropine. It is also injected into the umbilical cord of newborn infants in dose of 3 mg (1/20 gr.) to excite breathing but is frequently unsuccessful.

Lobeline stimulates and later paralyses ganglionic cell stations and this accounts for its dilator effect on the bronchioles; as Tinctura Lobelia Ætherea, it was formerly used in asthma.

GENERAL ANÆSTHETICS

General Anæsthetics produce total loss of consciousness with abolition of sensation and reflex action.

Alcohol.—Alcohol 96%, distilled from fermented saccharine liquids.

CHARACTERS.—A colourless, volatile liquid with spirituous odour and burning taste.

Preparations

1. **Alcohol 90%.**—Spiritus Rectificatus.
   94·7 Mils of Alcohol 95%, Dist. Water to 100.
2. **Alcohol 80%.**—84·2 Mils of Alcohol 95%, Dist. Water to 100.
3. **Alcohol 70%.**—73·7 Mils of Alcohol 95%, Dist. Water to 100.
4. **Alcohol 60%.**—63·2 Mils of Alcohol 95%, Dist. Water to 100.
5. **Alcohol 50%.**—52·6 Mils of Alcohol 95%, Dist. Water to 100.
6. **Alcohol 45%.**—47·4 Mils of Alcohol 95%, Dist. Water to 100.
7. **Alcohol 25%.**—26·3 Mils of Alcohol 95%, Dist. Water to 100.
8. **Alcohol 20%.**—21·0 Mils of Alcohol 95%, Dist. Water to 100.

Spiritus Methylatus Industrialis.—Methylated Spirit. Alcohol 95% containing 5% of wood naphtha.

CHARACTERS.—A colourless, volatile liquid; odour of spirit and wood naphtha, taste burning. The use of Industrial Methylated Spirit is permitted in the preparation of certain Liniments; and of certain Extracts used internally: in the latter case it must be eliminated from the final product.

Amount of Alcohol by Volume in various Fluids containing it:

Spiritus Rectificatus, 90%; Spiritus Vini Gallici (Brandy), 40%; Spiritus Frumenti (Whisky), 40%; Rum, 40%; Gin 40%; Liqueurs (Benedictine, Chartreuse, Cointreau, Curaçao, Grand Marnier, Kummel, Vieille Cure), 40 to 42·8%; (Cherry Brandy, Crême-de-Menthe), 28 to 31%; Cocktails, bottled, 22 to 26%; Port, Sherry, Tarragona, Madeira, Marsala, 18 to 21%; Vermouth, 16%; Champagne, 11 to 14%; Burgundy, Chianti, 10 to 13%; Hock, Moselle, Claret, 8 to 13%; Cider, 5 to 9%; Ale, Beer and Porter, 3 to 5%; Kumiss (made from milk), 1 to 3%.

ACTIONS AND USES

Externally.—Alcohol is a protoplasm poison. It is thus an **antiseptic** and is most powerful in 70 per cent. strength. It is used as a disinfectant for the skin and surgical instruments; also as a solvent for other skin antiseptics, e.g. Iodine and Picric Acid. Alcohol precipitates proteins and strengths above 50 per cent. act as **astringents** and harden the skin; they are used as lotions to harden the nipples during lactation, to prevent bedsores, and blistering of the feet from walking. Alcohol, owing to its astringent action, is also an **anhidrotic**, diminishing the excretion of sweat; for this purpose it is applied externally to check excessive perspiration in the hands, feet and axillæ. Solutions of Alcohol (30 to 40 per cent.) by their rapid evaporation act as **refrigerants**: they produce a sensation of cold, withdraw heat from the surface by evaporation, and lower the body temperature. Dilute alcoholic solutions, sponged on the skin, are therefore useful to reduce febrile temperature temporarily, and as compresses to allay sensations of heat, pain or itching, in skin eruptions, as well as to relieve neuralgia and headache. Conversely, if the evaporation of Alcohol be prevented, or if it be rubbed into the skin in strong solution (70 to 90 per cent.), it at first irritates the cutaneous nerves, causing redness, heat and pain, and then produces a slight local anæsthesia. It is therefore a **rubefacient** and **counter-irritant**, and liniments containing Alcohol, along with volatile oils, other irritants and soaps (e.g. Linimentum Aconiti, Belladonnæ, Camphoræ Ammoniatum and Saponis), are rubbed into the skin to increase the local circulation and to allay pain in parts where there is underlying inflammation, induration, stiffness, or pain; for example, in chronic rheumatism, laryngitis, bronchitis, pleurisy, etc., and in sprains. Alcohol (1 Mil of 60 per cent.) has been injected into sensory nerves to check neuralgia; this percentage blocks sensory, not usually motor, impulses, but regeneration occurs in about a year. Alcohol relieves pain in sensitive dentine by precipitating the proteins of the nerve fibrils, i.e. is an **obtundent**.

Internally.—The action of Alcohol on mucous membranes is similar to its effect on the skin. Its local action begins in the *mouth* with its characteristic pungent, stimulating effect on the mucous membrane, which increases **salivation**. Wines and other alcoholic liquids, consumed during meals, stimulate the sensory endings in the nose, tongue and palate. By virtue of their taste and bouquet they give relish to food, stimulate the flow of saliva and increase the appetite; thus they reflexly **improve the gastric functions**.

In the *stomach*: (1) Alcohol dilates the superficial vessels and stimulates the secretion of the gastric juice by an action on the mucous membrane, but, although the juice secreted contains the usual amount of hydrochloric acid, it contains a smaller proportion of pepsin. The optimum effect is obtained from about 10 per cent. strengths of Alcohol; proportions higher than this cause increased secretion of mucus. (2) Alcohol tends to decrease the rhythmic movements and to lower the tonus; in this way its **carminative action** is explained. (3) The digestive action of the gastric ferments is retarded even by small doses. The action of Alcohol on digestion depends on these opposing factors; but the total effect of a moderate dose, well diluted, is to **favour gastric digestion**. The effect is partly reflex in origin and due to the pleasant taste of the beverage; hence the value of a small amount of wine or wholesome ale taken with meals by debilitated or aged patients. In convalescence from fevers or other acute illness Alcohol is a valuable adjuvant to dietetic measures, particularly in the form of carbonated wines. These stimulate the appetite and the functions of the stomach, and spare carbohydrates, fats and proteins. The danger lies in excess or strong spirit; this causes a secretion of viscid mucus which impairs digestion, and is a common cause of acute or chronic dyspepsia. As it increases the acid secretion of the stomach, Alcohol should not be allowed in hyperacidity or gastric ulcer. (4) The **irritant action** of strong (20 per cent.) or more alcohol on the gastric wall **produces reflexly** through the medulla **stimulation of circulation and respiration.** The heart beats more rapidly and powerfully, and the blood-pressure rises somewhat owing to slight constriction of the systemic and splanchnic arterioles; but the cutaneous vessels dilate, and this effect gives rise to a subjective sensation of warmth. Respiration is also accelerated and may be deepened. Alcohol reflexly relieves palpitation and improves the feeble action of the heart in fainting, and vaso-vagal collapse.

In the *intestine,* Alcohol acts as a **carminative** by arresting spasmodic movements, and it is commonly used in the form of whisky or brandy to expel flatus and relieve the pain of colic. In the form of brandy or port it is often effective in checking neurotic or lienteric diarrhœa.

Absorption of Alcohol.—Alcohol is rapidly absorbed, passes into the blood unchanged, and is oxidized by the tissues. The maximal concentration of Alcohol in the blood occurs in from 1/2 to 2 hours after it is taken, and is proportional to the amount taken and. inversely proportional to the body weight. Foods, especially fats, inhibit intoxication by delaying the absorption of Alcohol, while large draughts of water or alcoholic liquor taken within 3 hours previously, accelerate the absorption. Alcohol is slowly oxidized at the rate of 0·185 c.c. per Kg. body weight per hour, i.e. an adult oxidizes about 10 c.c. (150 min.) per hour; it is therefore cumulative and repeated doses at less than 3-hourly intervals have an additive effect. Exercise increases the rate of oxidation of Alcohol only when the amount taken has been small.

Alcohol as a food.—Alcohol is oxidized in the tissues into carbonic acid and water, with perhaps an intermediate production of acetic acid. This oxidation yields heat and energy; and, in equal weights, Alcohol contains more energy—1 c.c. yields 7 calories

—than starch or sugar. Alcohol can act as a substitute for fats and carbohydrates in the diet, and it is common knowledge that alcoholics are often stout; it may be used to increase the caloric value of the diet in diabetes, as it does not increase the sugar excretion. Alcohol, however, **influences metabolism** in other ways. It is known that a diminution of fat or carbohydrate in the diet leads to increased protein autolysis and increased nitrogen excretion. Thus, if fat be withheld, the nitrogen excretion increases because the proteins are drawn upon to replace the deficiency of fat. The substitution of an equivalent food-value of Alcohol in such a case leads gradually to diminution in nitrogen excretion till the normal equilibrium is re-established. If Alcohol and fat both be given, the proteins are spared and the nitrogen excretion falls below normal. For its power of conserving the body proteins, Alcohol is frequently allowed in small doses during debilitating illnesses.

Small doses of Alcohol do not materially influence the gaseous exchanges in the lungs.

The action of Alcohol on the Nervous System.—The action of **Alcohol is depressant** to the nervous system in the reverse order of its evolution. It has been conclusively proved that Alcohol impairs concentrated attention, critical judgment, mental calculation and the accuracy of complex muscular actions. It depresses first the highest psychic faculties of criticism, shyness, anxiety and fear so that there results a **stage of apparent intellectual stimulation** in which the person becomes vivacious, converses more brilliantly and becomes unusually confident both of his decisions and his physical powers. Soon by depression of the intellect, judgment becomes defective and confused, therefore the speech lacks logical sequence, and, as the inhibitory centres become more depressed, argumentative loquacity develops and the unrestrained motor area is the reason for the gesticulation and motor excitement. The perceptive centres are next involved and the person, becoming oblivious of his surrounding, may at this stage fall asleep. If sleep does not supervene, the special senses become depressed, vision is defective, touch and muscular senses are impaired, so that movements become inco-ordinate and the sense of pain is abolished. Then from depression of the motor area the person becomes incapable of supporting himself and, finally, of moving. In deep alcoholic poisoning the spinal reflexes are lost and, from medullary depression, respiration is slow and stertorous, the skin cyanosed and the person comatose.

Actions on the Circulatory System.—In decerebrate animals, weak alcoholic injections increase the cardiac contractions because the Alcohol acts as a nutrient to the muscle, but strong solutions of Alcohol are direct depressants to cardiac muscle and quickly impair the contractility of the auricle and then of the ventricle. In man, the acceleration of the heart and rise in blood-pressure resulting from strong Alcohol are due to gastric irritation which reflexly lessens the vagus control and stimulates the vaso-motor centre. For its reflex stimulant effect on the heart, Alcohol in the form of whisky or brandy is a convenient, valuable and rapid means of improving the circulation in fainting, and moderate degrees of cardiac syncope or shock. In emergency, it will serve to ease the pain of effort angina.

Diaphoretic and Diuretic Actions.—Alcohol dilates the cutaneous vessels; to some extent this is again a reflex effect but it is also due to depression of the thermogenetic centre. The peripheral dilatation gives rise to a sensation of bodily warmth and comfort and to free perspiration in warm surroundings. The increased loss of heat lowers the body temperature and Alcohol is, therefore, an **antipyretic**. It is popularly used to avert chill following exposure and to promote perspiration at the onset of catarrhal infections. For these purposes it is more effective in the form of hot water with whisky (Toddy) or port (Negus) sweetened with sugar. Its use is, however, unwise if the patient is again to be exposed to low temperatures which will rapidly cool the body, and thus lower its resistance to bacteria and possibly originate lobar pneumonia. The diaphoretic effect is to some extent vicarious with the renal excretion and, in cool temperatures which prevent sweating, the excess of water taken with the Alcohol is excreted by the kidney; this explains the well-known **diuretic effect** of taking spirits, wines, and beer; gin contains some oil of juniper which irritates the renal epithelium. Diuresis is more marked with carbonated wines because carbon dioxide promotes the absorption of the Alcohol and water. The diuretic action is not utilized in therapeutics.

Action on Respiration.—Reflexly from gastric irritation, strong Alcohol accelerates respiration. On the other hand, if the centre be in a highly excited state, Alcohol in small doses often slows and steadies the breathing by so depressing the higher centres as to relieve the anxiety, distress and restlessness of the patient. It is with this objective, and also of inducing sleep to conserve the strength, that Alcohol is given in the early stages of lobar pneumonia, broncho-pneumonia, etc. Toxic doses of Alcohol are direct depressants to the respiratory centre and render breathing slow and stertorous.

Hypnotic Action.—The use of Alcohol as a depressant of the higher cerebral centres with a view to inducing sleep must be advised with caution. Sleeplessness due to overwork, worry, neuralgia, etc., is readily overcome by warm alcoholic drinks at bedtime, but the danger of commencing a habit must be considered and it is best to allow a definite amount of claret, port, or other alcoholic liquid for a restricted period only.

Excretion and Tolerance.—Alcohol is oxidized by the body at the rate of 10 c.c. per hour. Small amounts are excreted in the urine and the breath. The percentage in the urine is a little higher than, but runs parallel with, that in the blood. Both percentages have been suggested as means of estimating the degree of intoxication, but they are unreliable, as the cerebral action varies widely in different subjects. The tissues rapidly acquire increasing powers of oxidizing alcohol and a high degree of tolerance can be established and may persist for months after abstention.

Chloroformum.—Chloroform. Trichloromethane, $CHCl_3$, to which 1 to 2% of Ethyl Alcohol has been added. It should be kept in a cool dark place. It is prepared from Alcohol, Industrial Methylated Spirit, or acetone by the action of chlorinated lime and slaked lime: (1) $2C_2H_5OH + O_2 = 2CH_3CHO$ (aldehyde) $+ 2H_2O$. (2) $CH_3CHO + 3Cl_2 = CCl_3CHO$ (chloral) $+ 3HCl$. (3) $2CCl_3CHO + Ca(OH)_2 = 2CHCl_3 + Ca(COOH)_2$ (calcium formate).

CHARACTERS.—A colourless liquid, of characteristic odour and pungent sweet taste. *Solubility.*—Freely in alcohol and ether; 1 in 200 of water, in which it sinks. When exposed to light and air with no alcohol added, Chloroform decomposes into carbonyl chloride and chlorine, which are irritant when inhaled.

Dose.—*By mouth:*

Metric, 0·06 to 0·3 Mil; Imperial, 1 to 5 min.

Preparations

1. **Aqua Chloroformi.**—Chloroform, 0·25% in Water.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.
2. **Emulsio Chloroformi.**—Chloroform 5% with Liquid Extract of Quillaia and Mucilage of Tragacanth in Distilled Water.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.
3. **Spiritus Chloroformi.**—Spirit of Chloroform. Chloroform, 5% in Alcohol 90%.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.
4. **Tinctura Chloroformi et Morphinæ** (B.P.C.). *Not official.*—"Chlorodyne." Chloroform, 12·5; Ether, 3·125; Alcohol, 12·5; Morphine Hydrochloride, 0·229; Dilute Hydrocyanic Acid, 6·25;

Oil of Peppermint, 0·1; Liquid Extract of Liquorice, 12·5; Treacle, 12·5; and Syrup to 100.

Dose.—Metric, 0·3 to 0·6 Mil; Imperial, 5 to 10 min.

ACTIONS AND USES

Externally, if the vapour be confined or the Chloroform rubbed into the skin, it acts as an irritant, causing redness with a sense of heat and pain, followed by anæsthesia due to depression of the sensory nerve endings of the part. A similar effect is produced on exposed mucous membranes and it is used to allay the pain of caries or an exposed tooth-pulp. As a **rubefacient and counter-irritant** Chloroform may be applied on lint covered closely with a watch-glass, e.g. in localized neuralgia; or in the form of liniments containing it in combination with Belladonna and other anodynes which are used for the relief of lumbago, neuralgia, etc.

When given *internally* by the mouth, Chloroform has a hot, sweet taste which renders it useful in pharmacy to cover the nauseous, bitter and astringent tastes of many drugs. Like Alcohol, it causes reflex salivation; and in this way, as well as by a **carminative** and **sedative** action on the stomach, the Spiritus and Aqua are useful adjuvants to stomachic mixtures, relieve pain, vomiting and flatulence. In larger doses it gives rise to vomiting, which frequently occurs after anæsthesia, owing to its excretion in the breath. The Tincture of Chloroform and Morphine is a substitute for "Chlorodyne," a popular intestinal sedative and carminative, commonly prescribed in mixtures for fermentative diarrhœa.

A few drops of Chloroform inhaled from a piece of lint (quite apart from its action and use as a general anæsthetic) rapidly depress the sensory nerves in the bronchi, and may be employed with care to arrest spasm of the glottis, and acute asthmatical spasm. The Aqua is used as a vehicle in cough mixtures for the sedative effect of the Chloroform on the bronchial mucous membrane during its excretion by the lungs.

Chloroform as a General Anæsthetic.—Chloroform, if inhaled in the form of vapour freely mixed with air, reaches the tissues very rapidly. It requires 2 per cent. of Chloroform vapour in air to induce anæsthesia and about 1 per cent. to maintain it, while 3 to 4 per cent. in air will soon produce respiratory failure. A concentration of 0·02 per cent. in the blood and tissues is necessary for light anæsthesia; from 0·025 to 0·035 per cent. maintains surgical anæsthesia; whilst 0·04 to 0·07 per cent. can cause respiratory failure; the margin of safety is, therefore, small. The following description of the phenomena of anæsthesia has special reference to Chloroform, but it is also applicable to other general anæsthetics, particularly Ether, if the differences in action be noted.

1. **Phenomena of Chloroform anæsthesia.** (*a*) *First stage* of **irritation and blunted perception or analgesia.**—The inhalation of Chloroform irritates the nasal, laryngeal, and buccal mucous membranes, and may cause sneezing, coughing, and salivation; the irritation of the fifth nerve in the nose often causes, reflexly through the medulla, temporary cessation of respiration and momentary retardation of the heart. Imagination and the feelings are exalted but confused; there is a sensation of roaring in the ears; and vision, hearing and touch become confused and dulled. The pulse becomes more rapid, blood-pressure rises, respiration is slightly accelerated, the pupils dilate, and the face is flushed.

(*b*) The *second stage* is characterized by **depression of the higher cerebral centres,** and **unrestrained activity of the motor centres,** which are now deprived of the higher inhibitory control. Various inco-ordinate gesticulations, spasms, and reflex or protective struggling movements ensue; and the patient often becomes talkative although the speech is thick and ideas are confused. Respiration is irregular owing to the struggling; the pulse is accelerated; blood-pressure is raised, especially during periods of struggling; the pupils are dilated, the eyes move from side to side, and the skin is flushed or cyanosed. During this stage the patient is unconscious, and does not actually feel pain, but the reflexes, both spinal and medullary (vaso-motor and respiratory), are still present.

(*c*) *Third stage.*—With the onset of the **stage of surgical anæsthesia,** the muscular movements gradually diminish, the muscles relax and *reflex action is abolished,* the corneal reflex being one of the last to disappear. The pulse is slower and weaker; blood-pressure falls below normal; respiration is regular but slow and shallow, and often snoring owing to closure of the fauces by the relaxed tongue. The pupil becomes contracted as in sleep and fails to react to light; and the temperature of the body tends to fall from muscular quiescence. Anæsthetists divide the stage of surgical anæsthesia into four planes of increasing depth.

When the stage of surgical anæsthesia has been established, it is safe to operate. Prior to this, surgical interference with sensitive parts will excite reflex movements and may lead to reflex inhibition of the heart and respiration, or to ventricular fibrillation.

When operations are being performed on the rectum and genito-urinary organs, it is often necessary to push the Chloroform till the patient borders on the fourth stage, in order to abolish the reflexes and relax the sphincter muscles.

(*d*) *The fourth or danger stage.*—This is characterized by the onset of **paralysis of the medullary centres.** Depression of the respiratory centre results in weak, irregular, sighing, or triphasic respiration which may fail suddenly. The onset of asphyxia is indicated by sudden wide dilatation of the pupils and by cyanosis of the lips, ears and finger-nails. As the cardiac muscle is now seriously weakened, the pulse becomes feeble and irregular. The vaso-motor centre is depressed, and dilatation of the splanchnic vessels adds to the effect of cardiac weakness in lowering the blood-pressure; the skin appears pale and wax-like. In this stage the anal and bladder reflexes are abolished. Death may occur either from respiratory or cardiac failure.

2. **Analysis of the phenomena of Chloroform anæsthesia.**

(*a*) *Nervous system.*—The action of Chloroform on the nervous system closely resembles that of Alcohol. It rapidly depresses the higher psychic, inhibitory and perceptive centres, and the uncontrolled speech centre and motor area may initiate garrulous incoherent talk, gesticulation and resistant struggling. As the sensory area becomes depressed, pain is abolished, and soon from paralysis of the motor cortex the patient becomes quiescent, when it has been shown that the motor area is less sensitive to electrical stimuli. Abolition of the spinal-cord reflexes follows: the first to disappear are those of the back and limbs, then those of the abdomen and genital organs, next the corneal and light reflexes and, later, the sphincter reflexes of the bladder and rectum. Depression of the medullary reflexes occurs last. The **sensory neurons are paralysed before the motor**; because, if Chloroform be prevented, by removing the pia mater, from reaching a segment of the cord, stimulation of the intact sensory nerves of this segment although all other spinal reflexes have been abolished—will produce reflex contraction of muscles supplied by motor neurons in others parts of the cord which are under the influence of Chloroform.

Theories of Narcotic Action.—Many suggestions have been made to account for the action of the general anæsthetics and organic hypnotics. The *Meyer-Overton theory* takes as its basis the fact that all aliphatic compounds producing narcosis are easily soluble in fats and lipoids, and suggests that in the brain these compounds form with the lipoids of the nervous cells a loose combination, which temporarily inhibits the functions of the cells. This theory only explains why these drugs have an affinity for nervous tissue. Since anæsthesia is a temporary state, it is likely that the action is a physical rather than a chemical action, and there is evidence that their depressant effect on surface tension plays a part. Lipoid affinity and surface affinity concentrate the anæsthetic on the cell membranes and alter the cellular permeability. Initially, anæsthetic drugs increase the permeability which excites the cell; later the permeability is reduced and this seems to be the essential origin of the narcosis. The effect may also be dependent on alteration of the electrical potential of the cell or of the intracellular catalase enzymes.

(*b*) *Respiratory system.*—During the first stage, too strong an anæsthetic vapour may cause **temporary inhibition of respiration** reflexly from irritation of the fifth nerve endings; this is not usually troublesome, and careful administration will avoid it. In the second stage respiration is irregular during struggling, and, under careless administration, a series of **deep breaths may produce a high concentration of Chloroform in the blood** and cause severe depression of the respiratory centre. In the third stage **respiration is slow but shallow**, because Chloroform lowers the sensitiveness of the respiratory centre both to the sensory stimuli from the vagus and also to the chemical stimulus of the CO_2-tension in the blood; the CO_2-tension is also lowered owing to the quiescence of the body. The slowing becomes more pronounced as the anæsthetic is pushed, till the breathing gradually ceases.

(*c*) *Circulatory system.*—In the first stage, Chloroform vapour may reflexly, through irritation of the fifth nerve, excite the vagus centre or render it more sensitive to external stimuli, so that slowing or temporary inhibition of the heart may occur; a previous injection of Atropine, which paralyses the vagal endings, obviates this effect. Usually, in the early stages of anæsthesia, the heart rate is accelerated owing to excitement, and blood-pressure may rise from reflex stimulation of the vaso-motor centre. In the later stages the heart is gradually slowed and weakened by direct muscular depression, especially of the auricle. The blood-pressure falls, chiefly from direct relaxation of the arterial muscle, but Chloroform also depresses the vaso-motor centre and produces a **reversal of the normal vaso-motor reflex**, whereby a sensory stimulus, instead of producing a rise in blood-pressure causes a decided fall.

In light anæsthesia, two types of cardiac collapse may arise: (i) The **sympathetic type** occurs most frequently in nervous patients, whose blood already contains excess of Adrenaline. A sudden increase in the concentration of the Chloroform vapour weakens the heart muscle and also renders it highly sensitive to Adrenaline. Commonly, some sensory stimulus, e.g. too early incision, is the exciting factor; this, during light anæsthesia, causes a further output of Adrenaline which produces auriculo-ventricular fibrillation. This immediately arrests the circulation, the blood-pressure falls suddenly and after a few gasps respiration ceases. The only hopeful treatment is cardiac massage along with artificial respiration; injection of Adrenaline is obviously contra-indicated. (ii) The **vagal type**, which may follow a sudden intake of concentrated Chloroform vapour, and takes the form of inhibition of the heart due to stimulation (possibly reflex) of the vagus centre acting upon the already depressed and therefore sensitive cardiac muscle; the blood-pressure falls rapidly and respiration gradually ceases: this type is not usually alarming as the heart escapes from vagus control, and it can be prevented or treated by an injection of Atropine.

(*d*) *The Pupil.*—The pupil is dilated in the first and second stages reflexly from excitement. In the anæsthetic stage it is small; in the fourth stage it becomes widely dilated. Dilatation of the pupil, therefore, is a sign that the patient is having either too little or too much Chloroform; in the former case the dilated pupil reacts to light and often presages an attack of sickness; in the latter case, the widely dilated pupil does not react to light and is evidence of asphyxia.

(*e*) **The Uterus.**—The parturient uterus contracts freely in complete anæsthesia, with some loss of vigour and regularity.

3. **Delayed Chloroform poisoning.**—This condition may arise *gradually*—when the patient never recovers thoroughly from the anæsthetic but becomes gradually prostrate, delirious and comatose; or *suddenly*—when, after apparent recovery, there develops, within 10 hours to 6 days, acute delirium alternating with periods of stupor and coma. There is commonly vomiting of blood, jaundice, and hæmorrhage from the bowel; bile secretion is reduced and bile pigments may appear in the urine; examination of the blood will show hypoglycæmia and a lowered alkali-reserve; the urine contains acetone and diacetic acid, and, *post mortem*, the liver and other organs are found to be in a state of fatty degeneration. The condition is comparable with acute yellow atrophy and

diabetic ketosis. Such cases occur most commonly in children or after very prolonged anæsthesia. Excessive restriction of food, particularly carbohydrates, is a predisposing cause. Methionine is effective as a prophylactic and in treatment (*see* p. 200); casein digests or a high protein diet for some days before act also as protectives against hepatitis. Injections of Dextrose, Ringer-Lactate, or Sodium Bicarbonate assist in counteracting the ketosis.

4. **Uses of General Anæsthetics.**—General anæsthesia is employed: (i) In *operations attended with pain.* (ii) In *operations where muscular contraction or spasm has to be overcome*, reduction of herniæ, dislocations and fractures; catheterization. (iii) In *diagnostic manipulations*, bimanual palpation of the pelvis. (iv) In *conditions associated with excessive pain*, especially the passage of biliary and renal calculus. (v) In *parturition*, the degree of anæsthesia induced being generally light so as not to inhibit reflex contractions of the abdominal muscles until the passage of the fœtal head through the pelvis. (vi) In *spasmodic diseases*, such as tetanus, hydrophobia, uræmia, puerperal convulsions, status epilepticus, etc.

5. **Method of administration and precautions necessary for inducing anæsthesia.**—This practical subject must be learned by experience and the student must interpret every symptom of pharmacological significance because only thus will he appreciate accurately the condition of the patient at any moment.

The following practical points can be discussed but briefly:

(i) *Selection of cases.*—Chloroform must be given with great caution to the aged, to persons with myocardial weakness, to diabetic patients, to fat and anæmic persons, to epileptics, and to chronic alcoholics. For such patients, Nitrous Oxide, Ether or other anæsthetic is to be preferred. Operations on the mouth, nose or throat, with possible bleeding into the glottis, demand that the cough reflex should not be abolished.

(ii) *Preparation of the patient.*—No food should be given for at least four hours before the operation. Artificial teeth should be removed. To allay excitement Morphine with (to prevent salivation and cardiac inhibition) Atropine or Hyoscine are usually injected prior to the induction of anæsthesia. These "pre-medication" drugs also reduce the amount of anæsthetic necessary to maintain anæsthesia. The respiration and pulse should be carefully observed before commencing inhalation.

(iii) *Selection of the anæsthetic.*—The anæsthetic agents in general use at the present time are Nitrous Oxide, Nitrous Oxide with Oxygen, Ethyl Chloride, Ether, Chloroform, A.C.E. Mixture (Alcohol 1, Chloroform 2, Ether 3), and other mixtures containing Chloroform and Ether, Ethylene, Cyclopropane and Trichloroethylene. Chloroform, owing to its dangers, is generally avoided although convenient in general practice. Nitrous Oxide with Oxygen or Ether is to be preferred unless there be some special reason to the contrary. Mixtures, e.g. A.C.E., of liquid anæsthetics have the disadvantage that the composition of the inhaled vapour varies with temperature and cannot be estimated. It is a common practice to start with a rapidly acting anæsthetic and to replace it, when unconsciousness has been achieved, by a more slowly acting one, e.g. Nitrous Oxide–Ether sequence. The merits of Ethylene, Cyclopropane and Trichloroethylene are described later.

(iv) *Selection of the apparatus.*—Whilst elaborate inhalers are used in hospitals, simple apparatus may be equally safe, such as a handkerchief or piece of lint or flannel stretched over a wire frame, care being taken that with Chloroform, the vapour is diluted freely with air. For emergencies, a cylinder containing Carbon Dioxide (5 per cent. with Oxygen) and also solutions of Adrenaline, Methylamphetamine, Nikethamide or Leptazol, and Atropine, a hypodermic syringe, a pair of straight tongue forceps, and a tracheotomy tube should be at hand.

(v) *Position of the patient.*—The administrator must accommodate himself to the convenience of the operator. If possible, the recumbent patient's head is so placed on a pillow that the saliva may flow from the mouth instead of into the stomach, and that the tongue may not fall back and produce dyspnœa. The respiratory movements of the chest and abdomen must not be restricted by clothes, or bandages.

(vi) *Administration of Chloroform.*—The confidence of the patient should first be gained, whilst he is reassured and instructed how to breathe. When inhalation has commenced, the administrator must keep constant observation upon the respiration, pupils and pulse, which is accessible in the temporal or facial arteries. Chloroform should be dropped slowly but steadily on the mask (from 10 to 50 drops per minute), the interval between the drops being gradually shortened. The pouring on at intermittent intervals of a considerable quantity of Chloroform must, above all, be avoided. The head should be tilted to the side and the lower jaw supported to prevent closure of the glottis. When the patient is anæsthetized, the condition should be maintained by the smallest possible amount of the drug (about 5 to 10 drops per minute). A lighter degree of anæsthesia is permissible during child-birth, but deep anæsthesia is necessary for rectal operations. The loss of the corneal and light reflexes and stertorous breathing are generally employed as tests of insensibility, but reliance should not be placed upon a single sign.

(vii) *Complications and unfavourable symptoms.*—*Vomiting* is generally presaged by pallor of the face and a few deep inspirations. Care must be taken, by affording a free exit, that nothing is drawn into the larynx; the head should be thrown more over to the side, and the mouth opened by pressure on the symphysis, or a Mason's gag may be inserted between the teeth. Tracheotomy may be necessary if vomited matter be inhaled.

Lividity of the face and prolonged deep *stertor* indicate lack of Oxygen; the anæsthetic should be withheld and the patient allowed to breathe air. Mucus in the larynx may obstruct the free entrance of air.

Extreme pallor of the face is indicative of circulatory failure; the anæsthetic should be stopped, the head lowered and Atropine injected.

Shallow breathing, especially if intermittent, should be watched anxiously: it may be due to lack of the CO_2 stimulus or to severe depression of the centre. During anæsthesia, respiration may become shallow, or fail, from a train of circumstances, thus: overbreathing leads to excessive excretion of CO_2 and, this being the normal stimulus to respiration, there follows a period of very shallow breathing (acapnia) to which the depressant action of the anæsthetic on the respiratory centre also contributes. It should be noted that the slow and shallow respiration of the third stage is due to the fact that the anæsthetic renders the respiratory centre less sensitive both to the afferent vagal stimuli and to the CO_2 stimulus. Inhalations of Carbon Dioxide 5 per cent. with Oxygen will, however, increase the depth of respiration (*see* p. 139).

(viii) *After-treatment.*—Absolute quietness and closure of the eyelids often prevent sickness after operation. Recovery may be hastened by stimulating deeper respiration by means of Carbon Dioxide inhalations. The room should be cleared of the anæsthetic vapour as quickly as possible. Food should not be given within 3 hours after the operation, and not even then unless the patient desires it; and for the first 12 hours should be cool, and consist chiefly of soups and jellies, milk being avoided. Chloroform sometimes causes albuminuria, and its use in diabetes mellitus is risky because it increases the blood-sugar and favours ketosis.

(ix) *Excretion of Chloroform.*—Chloroform is excreted rapidly and almost wholly by the lungs. A small quantity is excreted in the urine and in the alimentary tract.

Æther Solvens.—Solvent Ether. Diethyl Ether. $(C_2H_5)_2O$.

CHARACTERS.—A colourless, mobile, inflammable liquid with characteristic odour.

Æther Anæstheticus.—Ether. Diethyl Ether. $(C_2H_5)_2O$. Made by distilling Ethyl Alcohol with Sulphuric Acid. (1) $C_2H_5OH + H_2SO_4 = C_2H_5HSO_4$ (sulpho-vinic acid) $+ H_2O$. (2) $C_2H_5HSO_4 + C_2H_5OH = (C_2H_5)_2O + H_2SO_4$.

CHARACTERS.—A colourless, very volatile and inflammable liquid; odour characteristic; taste, sweet and burning. *Solubility.*—1 in 8·5 of water. Miscible with Alcohol, Chloroform, and fixed and volatile oils. Store in a cool dark place.

Preparation

Spiritus Ætheris.—Ether, 33% in Alcohol 90%.
Dose.—Metric, 1 to 4 Mils; Imperial, 15 to 60 min.

ACTIONS AND USES

Externally.—Solvent Ether is used in Collodium Flexile to dissolve Pyroxylin (*see* p. 393). The use of Ether as a refrigerant local anæsthetic has been displaced by Ethyl Chloride sprays. If Ether is rubbed into the skin a **rubefacient** effect is produced, as with Chloroform. Ether dissolves the sebaceous secretion; and in the form of Ethereal Soap, it is a surgical detergent. Ether also dissolves cerumen in the ear.

Internally.—Ether has a burning, disagreeable taste, and causes more local irritation in the mouth and reflex **salivation** than Chloroform. In the stomach, Ether and the Spirit are irritants and local **stimulants** to the mucous membrane. They relax spasmodic contractions and are therefore used as **carminatives**, relieving pain and expelling flatulence. By gastric irritation, they act reflexly upon the circulation and respiration, as powerful and rapidly diffusible *reflex stimulants* and *antispasmodics.* The Spiritus is given in syncope from circulatory failure, to relieve palpitation and attacks of anginal pain; it is also useful in spasmodic cough, acute asthma, and in hysterical attacks.

Ether as a general anæsthetic.—Ether, when inhaled, is absorbed from the alveolar epithelium rapidly into the blood. Its action resembles that of Chloroform and only the important differences between the two substances require to be mentioned here. These are:

1. Ether requires to be inhaled in high concentration (12 to 14 volumes per cent.) in air for rapid induction and clinically about 6 per cent. is used to maintain surgical anæsthesia. When time is allowed for equilibrium to be established, from 4 to 4·5 per cent. in air will maintain surgical anæsthesia while 7 to 8 per cent. can produce respiratory failure. From 1½ to 2 fluid ozs. are required to induce anæsthesia and about 6 fl. oz. per hour to maintain it. The blood and tissues in light anæsthesia contain about 0·1 per cent. of Ether, in surgical anæsthesia from 0·13 to 0·14 per cent., while respiratory depression occurs at about 0·16 to 0·17 per cent. These figures show that the margin of safety with Ether is greater than that with Chloroform.

2. With Ether the stage of excitement is more protracted; there is more struggling; the degree of anæsthesia is less profound; and muscular relaxation less complete. As Ether is given with relatively less air, cyanosis is more common than with Chloroform. Ether is three times less depressant to the cerebrum, cord, and medulla (respiratory centre) and is thus safer than Chloroform.

3. Ether has twenty-five times less depressant action on the heart than Chloroform. In the stage of surgical anæsthesia, the pulse is usually more rapid and stronger; the blood-pressure is either normal or slightly increased, particularly if the air supply is much reduced; the face is flushed from dilatation of the superficial vessels and bleeding is more profuse under Ether. Cardiac syncope is very rare and even when the respiration is failing from overdosage with Ether, the pulse and blood-pressure may be practically normal. Ether is, therefore, much the safer anæsthetic for cardiac cases.

4. Ether has a less pleasant odour and causes more irritation of the air-passages and more salivation than Chloroform.

5. The after-effects of Ether, in the form of sickness and bronchial catarrh or even pneumonia, are more common and severe than those of Chloroform.

6. Ether convulsions of epileptiform type may occur during deep anæsthesia in young persons who are febrile and septic; they are preceded by dyspnœa and cyanosis, and commence with twitching of the eyelids and facial muscles but soon spread over the body; in many cases, they are fatal. Their origin is obscure; they may occur with other anæsthetics. The anæsthetic must be stopped, Oxygen is not very helpful but Thiopentone will control them if given early.

Administration.—Ether may be given by means of a cone-mask or cone-shaped towel with a restricted air inlet, and by pouring 4 fl. dr. of Ether on the absorbent surface; or, like Chloroform, by the open method, which avoids the sense of suffocation and cyanosis; but the Ether requires to be dropped on at the rate of about 2 to 3 fl. dr. per minute. Others prefer to give Ether in closed inhalers with restricted air supply, which latter accounts for the flushing or cyanosis of the face and for the increased depth of respiration and full pulse. Ether anæsthesia can be induced rapidly by use of an inhaler with a rebreathing bag of 4 to 5 litres' capacity, to which at first mixtures of 5 to 6 per cent. CO_2 in Oxygen, to produce deep breathing, are added, and then Ether, previously vaporized, in high concentration so as to raise the amount in the blood quickly to the anæsthetic percentage. By these means full anæsthesia is attained rapidly and the excitement stage almost eliminated; breathing is regulated by adding CO_2 and O_2 when required, while recovery is hastened by promoting deep breathing with this gaseous mixture.

In choosing between Ether and Chloroform, preference must be given to the *safer anæsthetic*, and therefore Ether is very extensively used. In certain circumstances Chloroform is preferable, such as for operations upon the mouth, because Ether causes profuse secretions of ropy mucus; in operations where a diathermy knife might come in contact with the Ether vapour and ignite it; in operations on the brain or where much hæmorrhage is anticipated because Chloroform lowers blood-pressure; and in parturition, where profound anæsthesia is unnecessary. Infants bear Chloroform better, and their delicate respiratory passages are less irritated by it than by the pungent vapour of Ether; but Chloroform is not to be regarded as a specially safe anæsthetic for children.

Æther Vinylicus.—Vinyl Ether. Vinesthene. $(CH_2{:}CH)_2O$. Divinyl Ether containing 4% of dehydrated alcohol and not more than 0·01% of phenyl-α-naphthylamine or other stabiliser to prevent polymerization.

CHARACTERS.—A colourless, inflammable liquid with a smell like garlic and may show a purplish fluorescence. Containers are of not more than 200 Mils capacity, and it should not be used if its container has been opened for more than 48 hours, as formaldehyde may form.

ACTIONS AND USES

Vinyl Ether (3 to 6 Mils) induces anæsthesia in one minute and, although causing some salivation, it does not irritate the air-passages nor impair circulation or respiration. Recovery takes place in about two minutes, vomiting is rare but there is a risk of liver damage if it is used for more than 1½ hours. A mixture of Vinyl Ether 1 with Ether 3 on an open mask induces anæsthesia rapidly and with adequate muscular relaxation for short operations, but the use of a closed inhaler with Oxygen is preferable and, for longer operations, an absorbent for Carbon Dioxide is required. It is advocated for rapid inductions, short minor or dental operations, obstetrical practice and as a supplement to Nitrous Oxide and Oxygen.

Æthylis Chloridum.—Ethyl Chloride. C_2H_5Cl.

CHARACTERS.—Gaseous at normal temperatures and pressure, but usually supplied condensed in glass phials into a colourless, mobile, inflammable and very volatile liquid. Odour pleasant, ethereal; taste burning.

Dose (*not official*).—*By inhalation:*

Adults. **3 to 5 Mils (45 to 75 min.).**
Children. **1 to 3 Mils (15 to 45 min.).**

ACTIONS AND USES

Externally.—Its low boiling-point (12°C.) renders Ethyl Chloride a very rapid **local anæsthetic** by freezing for superficial surgical operations, and for removal of front teeth. Care must be taken to avoid long application, which causes sloughing; thawing is painful.

Inhalation.—Ethyl Chloride is employed as a **general anæsthetic** for operations of short duration. It is administered from a closed inhaler; anæsthesia is induced in ½ to 1 minute, and lasts about 1½ minutes; recovery occurs in about 1 to 2 minutes. It may also be given by the "open" method, using 7 to 8 Mils for an adult. It is used in place of Nitrous Oxide for the removal of teeth, for brief operations, and prior to Ether and Chloroform administration as it shortens the period of induction. *Ethyl Chloride cannot compare with Nitrous Oxide in safety*; it is a depressant to cardiac muscle, and headache and sickness are frequent after its use.

Nitrogenii Monoxidum.—Nitrous Oxide. Laughing Gas. N_2O. Made by heating Ammonium Nitrate to 178° C. and washing the gas. $NH_4NO_3 = N_2O + 2H_2O$.

CHARACTERS.—A colourless, inodorous gas. It is provided for use condensed into a liquid, in iron cylinders, whence it is allowed to escape into an indiarubber bag. The cylinders should be painted *black* with the name of the gas painted or indelibly stamped on the body and the name or formula on the shoulder and valve; the connecting tubing should be *black*.

ACTIONS AND USES

Nitrous Oxide Gas, being soluble about 1 in 2 of the plasma, is rapidly absorbed from the lungs and, if administered from an inhaler along with air, it produces a stage of motor excitement with possibly hilarious laughter; the person behaves as if intoxicated, speech is confused, movements are unsteady and sensation is dulled.

Nitrous Oxide acts as a **depressant to the cerebral centres** and is a **general anæsthetic.** If the *undiluted gas* be inhaled it produces a sensation of rumbling in the ears, mistiness of vision and of falling through space; within about a minute complete unconsciousness results with abolition of the sense of pain, loss of reflexes, but with incomplete muscular relaxation. When the patient is fully anæsthetized, the corneal reflex is absent but, owing to the deprivation of Oxygen, there are definite signs of asphyxia, e.g. facial cyanosis, slow and stertorous respiration, a slow and full pulse with raised blood-pressure, dilated pupils and possibly some muscular twitching. On removing the mask these asphyxial symptoms quickly vanish; the **anæsthesia lasts about 45 seconds** and recovery is complete in from 1 to 3 minutes; after-effects are very rarely experienced.

Pure Nitrous Oxide is used very largely as an anæsthetic in dentistry to permit painless extraction of teeth and for minor surgical operations. The average amount required is from 2 to 3 gallons. It is also employed as a preliminary to Ether anæsthesia, and the "Gas–Ether Sequence" is an excellent method for major operations, as it induces rapid anæsthesia without a stage of excitement. Operations requiring several minutes may be performed by allowing intermittently—about 1 in 5—a breath of air. Although pure Nitrous Oxide Gas is an extremely safe anæsthetic, it should not be used for patients having a high blood-pressure, myocarditis or valvular disease.

Mixtures of Nitrous Oxide and Oxygen are used to enable more prolonged operations to be performed without asphyxial symptoms. Special apparatus is used so that the gases may be mixed in any proportion. Induction is carried out by pure Nitrous Oxide, or with the addition of 2 per cent. of Oxygen, and then the percentage of Oxygen is increased until cyanosis is eliminated, which occurs usually with a mixture of 90 per cent. Nitrous Oxide and 10 per cent. of Oxygen; but as the proportions vary between 5 and 15 per cent. of Oxygen they require to be carefully balanced.

Under Nitrous Oxide and Oxygen anæsthesia, breathing is slow, regular and snoring, the pulse more rapid and the blood-pressure somewhat increased; and, although the reflexes are almost abolished, the muscular relaxation is not complete. This method is, however, the safest anæsthetic method except for major operations, when Ether may be used as a supplementary anæsthetic.

Æthylenum.—Ethylene. Olefiant Gas. $CH_2 : CH_2$.

CHARACTERS.—A colourless, inflammable gas; odour and taste sweet, ethereal, rather objectionable. Obtainable liquefied in cylinders. The body of the cylinder should be painted *mauve* with the shoulder *red* and the name of the gas indelibly stamped on the body and the name or formula on the shoulder and valve. With 40% of air or Oxygen forms an explosive mixture, hence it should not be used near a cautery or flame.

ACTIONS AND USES

A mixture of Ethylene 90 per cent. with Oxygen 10 per cent. **induces surgical anæsthesia** almost (3 to 5 minutes) as rapidly as, and more effectively than, Nitrous Oxide, without causing cyanosis, dyspnœa or rise of blood-pressure but providing fairly complete muscular relaxation. When anæsthesia is established, it can be maintained by a mixture of 80 per cent. Ethylene and 20 per cent. Oxygen. In Ethylene anæsthesia, respiration is regular but somewhat slow; there is an absence of pulmonary irritation or salivation and the pulse remains about normal. Recovery occurs very rapidly in from 2 to 5 minutes but vomiting is a frequent sequel. American experience indicates that Ethylene gives a better surgical anæsthesia than Nitrous Oxide and Oxygen and without the objectionable effects of Ether.

Cyclopropanum.—Cyclopropane. Trimethylene. $\overline{CH_2 .\ CH_2 .\ CH_2}$.

CHARACTERS.—A colourless, inflammable gas, with odour like Chloroform; mixtures with air or oxygen are explosive. It is compressed in cylinders of which the body should be painted *aluminium* and the shoulder *red*; and the name of the gas indelibly marked on the body with the name or formula on the shoulder and valve; the connecting tubing should be *aluminium-coloured* with a *spiral red* line.

ACTIONS AND USES

Cyclopropane induces anæsthesia rapidly without any irritation. Percentages of 7·5 to 10 will maintain light anæsthesia, and of 15 to 20 per cent. deep anæsthesia with good muscular relaxation, while 42 per cent. will produce respiratory arrest. As the gas is expensive, it is usually given along with pure Oxygen by using a Carbon Dioxide absorption technique. Recovery is rapid and after-effects uncommon but during deep anæsthesia watch must be kept for failing respiration, and for a rapid and irregular or very slow pulse, all of which are danger signals. Cyclopropane has proved very valuable for major thoracic and abdominal operations, and for patients with pulmonary infections, heart disease or shock. Its advantages are that it is not irritant, is used with a high percentage of Oxygen and induces quiet breathing; its disadvantages are that it causes capillary oozing and may produce post-operative collapse with low blood-pressure (Cyclopropane shock).

Trichloroæthylene.—Trichloroethylene. Trilene. $CHCl : CCl_3$.

CHARACTERS.—A colourless, mobile liquid of low volatility and an odour like Chloroform but less pungent. Decomposes in bright light in air, and Thymol 0·01% is usually added as a preservative. It is coloured blue to distinguish it from Chloroform.

ACTIONS AND USES

Trichloroethylene is a general anæsthetic which is pleasant to inhale and rapidly induces in the first stage general analgesia without irritant effects or increased salivary or bronchial secretion, but early cardiac arrhythmia is fairly common; occasionally, second-stage excitement occurs with panting respiration; in the stage of surgical anæsthesia, abdominal muscular relaxation is incomplete, the pulse and respiration are commonly increased in rate, but the skin vessels are not dilated; hence capillary oozing does not occur as with Ether or Cyclopropane. After-effects, headache, mental confusion, nausea and vomiting, are common but usually slight.

Trichloroethylene is not sufficiently volatile for open-mask administration; it can be inhaled in sufficient concentration to induce general anæsthesia from the bottle of a "draw over" apparatus and, by regulated partial rebreathing, surgical anæsthesia can be maintained with about 13 c.c. per hour. It is used mainly as an adjuvant to gas and oxygen anæsthesia. It must not be used by the soda-lime closed-circuit technique because the heat decomposes it into dichloroacetylene which causes nerve paralyses.

Trichloroethylene is indicated for minor surgery, for operations involving diathermy, e.g. in thoracic surgery, and in superficial operations, e.g. breast, to obviate excessive bleeding. Inhalers, designed for self-administration by patients, e.g. during childbirth, are available.

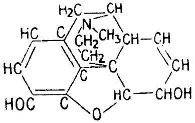
ANODYNE NARCOTICS

Anodyne narcotics are drugs which relieve pain and usually cause deep sleep. They are also termed pain-relieving or Anodyne Hypnotics.

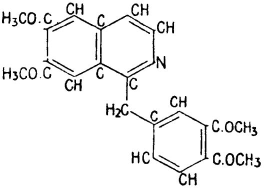
Opium.—Opium. The juice obtained by incision from the *unripe* capsules of Papaver somniferum, N.O. Papaveraceæ, the White Poppy, dried by spontaneous evaporation.

CHARACTERS.—Irregular dark-brown masses, covered with poppy leaves or seeds of Rumex. When fresh, plastic; becoming harder on keeping. Odour strong, characteristic; taste bitter.

COMPOSITION.—Opium contains, in moist condition, not less than 9·5% of anhydrous *Morphine; other alkaloids*; and resin, gum, sugar, odorous principles, and other constituents of plants. The *most* important principles are:



Morphine



Papaverine

1. *Phenanthrene Alkaloids:* Morphine, $C_{17}H_{17}NO(OH)_2$, 10 to 17%; Codeine, $C_{17}H_{17}NO(OH)(OCH_3)$, 0·3 to 4%; Thebaine, $C_{17}H_{17}NO(OCH_3)_2$, about 0·3%. 2. *Isoquinoline Alkaloids:* Narcotine, $C_{19}H_{14}(OCH_3)_3NO_4$, 2 to 7%; Papaverine, $C_{16}H_9(OCH_3)_4N$, 0·5 to 1%; Laudanosine, $C_{16}H_{12}(OCH_3)_4N.CH_3$; Narceine, $C_{22}H_{27}NO_8$; and Hydrocotarnine, $C_{12}H_{15}NO_3$; also Cryptopine, Codamine, Laudanine, Gnoscopine, etc. 3. *A neutral principle:* Meconin, $C_{10}H_{10}O_4$. 0·1 to 0·3%. 4. *Organic Acids:* Meconic Acid, $C_7H_4O_7,3H_2O$, 4 to 8% and Lactic Acid, 1·25%.

VARIETIES.—*Smyrna, Turkey* or *Levant* Opium, which is best, appears in round or flat masses, about 1,000 G in weight, covered with poppy leaves and fruits of Rumex. *European* Opium from the Eastern Balkans is similar. *Egyptian* Opium appears in reddish flattened cakes. *Persian* Opium is in brick-shaped masses wrapped in red paper. *Indian* Opium is in cubical blocks covered with oiled paper.

Incompatibilities of Opium.—The alkaloids are precipitated by lead acetate and other soluble salts of heavy metals, and by tannic acid and alkalis.

Opium Pulveratum.—Powdered Opium. Pulvis Opii. Dried Opium in fine powder adjusted, if necessary, by adding Lactose, to contain 10% of anhydrous Morphine.

CHARACTERS.—A light-brown powder, odour and taste characteristic. 200 mg (3 gr.) contains 20 mg (3/10 gr.) Morphine.
Dose.—Metric, 30 to 200 mg; Imperial, 1/2 to 3 gr.

Preparations

1. **Tinctura Opii.**—Laudanum. Opium, extracted with boiling Distilled Water and Alcohol 90% and standardized to contain 1% of Morphine. 2 Mils (30 min.) contain 20 mg (1/3 gr.) Morphine.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.

2. **Tinctura Opii Camphorata.**—Tinctura Camphoræ Composita, Paregoric. Tincture of Opium 5%, Camphor 0·3%, with Benzoic Acid, and Oil of Anise in Alcohol 60%. 4 Mils (60 min.) contain 2 mg (1/30 gr.) Morphine.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

3. **Pulvis Cretæ Aromaticus cum Opio.**—Powdered Opium 2·5% in Aromatic Powder of Chalk. 4 G (60 gr.) contain 10 mg (1/7 gr.) Morphine.
Dose.—Metric, 0·6 to 4 G; Imperial, 10 to 60 gr.

4. **Pulvis Ipecacuanhæ et Opii.**—Pulvis Ipecacuanhæ Compositus. Dover's Powder. Powdered Opium 10% with Ipecacuanha 10% in Lactose. 0·6 G (10 gr.) contains 6 mg (1/10 gr.) Morphine.
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

5. **Tabellæ Ipecacuanhæ et Opii.**—Dover's Powder 0·3 G (5 gr.) in each.

6. **Tabellæ Acidi Acetylsalicylici cum Ipecacuanha et Opio.**—Acetylsalicylic Acid and Dover's Powder of both 0·162 G (2½ gr.) in each.

Morphinæ Hydrochloridum.—Morphine Hydrochloride. $C_{17}H_{19}NO_3$, $HCl,3H_2O$. The hydrochloride of an alkaloid, Morphine, obtained from Opium.

CHARACTERS.—White, acicular crystals; taste, bitter. *Solubility.*—1 in 25 of water. *Tests.*—Morphine salts give with HNO_3 an orange-red colour; with solution of Fe_2Cl_6, a dull blue; with dilute solutions of Potassium Ferricyanide containing one drop of Fe_2Cl_6 solution, they give a bluish-green colour; and with H_2SO_4 and a drop of Formalin, they give a purple colour. *Incompatibles.*—Alkalis; salts of heavy metals; and vegetable astringents.
Dose.—Metric, 8 to 20 mg; Imperial, 1/8 to 1/3 gr.

Preparations

1. **Liquor Morphinæ Hydrochloridi.**—Morphine Hydrochloride, 1%; Dilute Hydrochloric Acid, 2% with Alcohol 90%, and Distilled Water. 2 Mils (30 min.) contain 20 mg (1/3 gr.) Morphine Hydrochloride.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.

2. **Suppositoria Morphinæ.**—Morphine Hydrochloride, 15 mg. (1/4 gr.) with Oil of Theobroma in each.

3. **Trochiscus Morphinæ et Ipecacuanhæ.**—Each contains 2 mg (1/32 gr.) of Morphine Hydrochloride, and 6 mg (1/10 gr.) of Ipecacuanha in the Lozenge Basis.

Morphinæ Sulphas.—Morphine Sulphate. $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$.

CHARACTERS.—Acicular crystals, or powder; taste bitter. *Solubility.*—1 in 24 of water, solution neutral.

Dose.—Metric, 8 to 20 mg; Imperial, 1/8 to 1/3 gr.

Preparations

1. **Injectio Morphinæ Sulphatis.**—A sterile solution in Water for Injection, labelled with the amount in a suitable dose volume.

Dose.—*Of Morphine Sulphate, by subcutaneous injection:*

Metric, 8 to 20 mg; Imperial, 1/8 to 1/3 gr.

2. **Injectio Morphinæ et Atropinæ.**—Atropine Sulphate 0·06% Morphine Sulphate 1% in Water for Injection. 1 Mil (15 min.) contains 0·6 mg (1/100 gr.) Atropine Sulphate and 10 mg (1/6 gr.) Morphine Sulphate.

Dose.—*By subcutaneous injection:*

Metric, 0·5 to 1 Mil; Imperial, 8 to 15 min.

ACTIONS AND USES

Opium and its preparations owe their actions mainly to the alkaloid Morphine; Opium preparations, being more slowly absorbed, possess more local action upon the alimentary tract but act less quickly on the cerebrum and medulla than Morphine. Further, since Opium contains other alkaloids, some of which (Thebaine, Narcotine, Codeine) augment spinal reflexes, the crude drug is less sedative to the central nervous system than Morphine.

Externally.—Opium is sometimes used in liniments, plasters and ointments to relieve superficial pain, but this is irrational because Morphine has no depressant action on sensory nerve endings and is only very slightly absorbed from the skin; its application to the conjunctiva, mucous membranes or the tooth-pulp as an anodyne is also irrational.

Internally.—In the *mouth*, Morphine has no local action. The dryness of the mouth and throat which follows after its absorption is due to depression of the secretory centres for the salivary and mucous glands.

In the *stomach*, Morphine has important actions: (1) it causes **contraction of the pyloric sphincter** which results in passive dilatation of the fundus; this action retards the emptying of the stomach for as much as six hours; (2) by a direct action on the gastric muscle, it increases its tone and thus **diminishes the amplitude of the gastric movements**; (3) after absorption and by central depression, Morphine **diminishes the sensation of hunger,** lessens appetite and **relieves gastric pain.** Morphine is said to decrease gastric secretion but this effect is unimportant.

Occasionally, and more commonly after a hypodermic injection of Morphine, nausea and vomiting may occur; this is due to direct stimulation of the vomiting centre; but it is followed by depression of the centre.

Morphine and Opium are **therapeutically valuable as gastric sedatives.** They are employed to relieve pain and to rest the stomach in acute gastric catarrh resulting from irritant foods or poisons, in gastric ulcer, in carcinoma, and in reflex vomiting from abdominal disease. Although not a direct hæmostatic, Opium, by rendering the stomach—and the excited patient—quiescent, promotes the arrest of gastric hæmorrhage. In the treatment of subacute and chronic dyspepsia, Opium is often given along with Bismuth, but it should be used in small dosage, particularly if food is being allowed, on account of the delayed emptying of the stomach.

In the *intestine*, Morphine or Opium is **sedative and constipating.** This action depends upon several factors: (1) Delayed transmission of food from the stomach occurs owing to the **contraction of the pyloric sphincter**; (2) **increased tone in the intestinal muscle** of the jejunum and ileum; (3) **contraction of the ileo-cæcal sphincter**; (4) increased and **spastic tone of the colon**; (5) contraction of the internal anal sphincter; (6) **relief of intestinal pain** by the cerebral action of Morphine.

The first five actions are exerted directly upon the involuntary muscle. Intestinal peristalsis is diminished by Morphine because the slower transmission of food from the stomach lessens the distension stimulus upon the intestinal wall and, as the intestinal tone is augmented, the peristaltic waves have a reduced amplitude. The fact that irritant purgatives fail to excite peristalsis when given with Opium suggested that Morphine paralysed the sensory side of the nervous reflex in Auerbach's and Meissner's plexus, but recent work favours the view that Morphine increases the tone of the whole—small and large—intestine so that the peristaltic waves are of smaller amplitude.

The total effect is to lengthen the time for the transit of the intestinal content to about twice the normal, retardation being most marked in the colon. The **slower transmission permits of increased absorption of water from the contents** and since Morphine by central action also reduces the intestinal secretions, the ultimate result is a more solid fæcal mass and the symptom of persistent constipation. The greater constipating effect of Opium compared with Morphine may be due to the direct depressant action of Papaverine and Narcotine on the peristalsis of intestinal muscle.

Rarely as an idiosyncrasy in man, Morphine when injected may cause, as in some animals, a brisk purgation prior to intestinal quiescence.

Morphine contracts the sphincter of the common bile-duct.

The **therapeutic applications** of the actions of Morphine and Opium **as sedatives to intestinal movements** and abdominal pain are very extensive, but they must be used with discretion. Opium is an obvious treatment for **diarrhœa**, but it should not be prescribed until irritant or toxic matter has first been removed from the bowel by purgation. With this reservation, Opium is valuable to check unusually frequent or fluid motions in enteritis following irritants or intestinal fermentation, in cholera, typhoid fever and tuberculous enteritis. For such purposes it is best prescribed as Powdered Opium or as the Pulvis Cretæ Aromaticus cum Opio, the latter being very suitable for infantile diarrhœa; pills containing Lead Acetate or powders containing Catechu, Krameria or Kino with Opium are advantageous in severe cases. For the relief of intestinal colic, Opium should be prescribed along with carminatives; a useful preparation is the Tinctura Chloroformi et Morphinæ (B.P.C.), which is an imitation of "Chlorodyne."

Opium is also **valuable to relieve pain** in strangulated hernia, intestinal obstruction, peritonitis, visceral perforation and abdominal wounds. As it may mask guiding symptoms, it should be avoided, unless the patient be in agony, until a satisfactory diagnosis has been reached.

When introduced into the rectum as the Suppository or by enema, Opium, by a local action, diminishes movement in the rectum and depresses the defecation reflex. The Suppository may serve to produce quiescence of the rectum after local operations or for internal hæmorrhoids and anal fissure, but the Opium relieves the pain only after its absorption.

Action on the Cerebrum.—After absorption Morphine **depresses the perceptive and sensory areas** of the cerebrum and **relieves pain.**

Small doses of Morphine render the cerebrum less sensitive to external impressions and, in consequence, there may be a stage of apparent stimulation when the person feels happy and comfortable, and exhibits vivacity of speech and behaviour with increased brilliance of imagination; the face appears flushed, the eyes more brilliant and the intellect seems exalted. Even at this stage, however, there is generally some perversion of thought which lacks logical sequence and the imagination becomes extravagant and uncritical, as in dreams. Such symptoms are more common in addicts or in persons of highly imaginative temperament.

Direct signs of the depressant action on the perceptive and sensory centres soon appear; the person becomes less influenced by—and takes little interest in—his surroundings, afferent impulses make less impression upon his cerebrum and the sensation of pain is dulled while that of touch becomes less discriminating. The type of pain which Morphine relieves is that of a dull recurrent or persistent type.

The decreased sensitiveness of the cerebrum to afferent impulses is a condition which promotes drowsiness and sleep. But at this stage any sudden sharp sensory stimulus or pain will arouse the patient, and it can then be proved that the intellect and motor area remain unimpaired; the patient will answer questions correctly, but does so very slowly because Morphine lengthens the cerebral reaction time to stimuli and retards co-ordination in the cerebrum; the movements also remain perfect but they are performed in a lethargic fashion. Left undisturbed, the patient relapses into heavy sleep in which the respirations are slow and deep and the pupils much contracted.

If the dose be large (1/2 gr.) the stage of exhilaration is entirely absent, the sensory area is speedily depressed, pain is relieved and sleep will result in about quarter to half an hour after the drug has been given. *Toxic doses* produce a deep comatose state from which the patient can be roused only by severe sensory stimulation, e.g. flagellation; even in this state, when aroused, he can still control his muscular movements. The pupils are contracted to "pin-hole" size, the face is now pale and cyanosed, respiration is extremely slow, and becomes weaker; death results from respiratory paralysis.

Use as an Anodyne.—The great value of Opium or Morphine as a **central anodyne** or agent **for relieving pain** depends on its selective action upon the sensory area in doses which do not seriously depress the medullary centres. There are few kinds of pain which Morphine does not relieve or mitigate, but it is most effective in checking pain of a constant character; sudden exacerbations of pain are perceived but their acuteness is dulled. In practice a hypodermic injection of Morphine Hydrochloride is the most rapid and effective way of affording relief in painful conditions.

Morphine is appropriately and essentially used to relieve the distress and pain of coronary thrombosis or occlusion, malignant disease, severe injuries, fractures, dislocations and acute gout, and during the passage of renal or biliary calculi. In abdominal disease, Morphine should be withheld, or given in small amounts, so long as the diagnosis is uncertain, *unless* the distress or shock of the patient renders it necessary. It is valuable to relieve the nervous collapse consequent on the severe pain of strangulated hernia, peritonitis, appendicitis and intestinal obstruction.

As a **hypnotic** the use of Opium or Morphine should be restricted to cases where sleeplessness is due to severe pain, when Morphine is far superior to the anodyne antipyretics or organic hypnotics. Morphine is occasionally useful in the insomnia due to restlessness and anxiety at the commencement of acute febrile illnesses, lobar pneumonia and in mental diseases. Morphine should be avoided, owing to the risk of producing habit, in the insomnia of overwork, worry or neuralgia. In the sleeplessness due to pain or anxiety during heart disease, Morphine is valuable as it has no depressant action on the heart but affords relief from restlessness and palpitation.

Its powers of depressing the perceptive and sensory areas renders Morphine valuable as a **pre-anæsthetic hypnotic**. Given about half an hour before an operation, it relieves the patient's anxiety, dulls his impressions of the preparatory events and renders the induction of anæsthesia more easy. Further, it has been shown that **Morphine potentiates the action of a general anæsthetic** so that less of this is necessary to maintain an adequate degree of anæsthesia. Before anæsthetics, it is often given in combination with Atropine or Hyoscine, both of which reduce salivary and bronchial secretions and also minimize the risk of cardiac inhibition through the vagus.

Actions on the Medulla.—The medullary centres are influenced selectively by Morphine. **Morphine depresses the respiratory centre** and renders its less sensitive to afferent stimuli through the vagus, with the result that breathing becomes progressively slower. Morphine only lessens or partially depresses the responsiveness of the centre to the carbon-dioxide stimulus, which will still increase the depth but rarely the rate of respiration; respiration, therefore, becomes progressively deeper. The increased depth does not, however, compensate for the slowing, and symptoms of anoxæmia or asphyxia appear, e.g. cyanosis; later the respiration becomes weak or shallow, occasionally with periodic or Cheyne-Stokes breathing, and death results from paralysis of the centre. The related **cough centre** is also rendered less sensitive to afferent impulses from the sensory vagal endings and impairment or even abolition of the cough reflex may result.

The *vagus and vaso-motor centres* are not influenced directly by Morphine; in poisoning, the cardiac rhythm is slowed and blood-pressure raised but these effects are secondary to the onset of asphyxia. The *vomiting centre* is at first stimulated, and this explains the nausea and vomiting which occasionally follow an injection of Morphine; later the centre is depressed and, in poisoning, it may fail to respond to irritant reflex emetics in the stomach or to Apomorphine. The *oculomotor centre* is stimulated by Morphine, and this is the cause of the constriction of the pupil (pin-hole pupil), which is a characteristic of its action in man; but when asphyxia supervenes the pupil dilates.

Uses in Respiratory Disease.—Although Morphine has a powerful effect through its depression of the respiratory and cough centres in relieving **dyspnœa and cough**, it must be used with forethought because these symptoms are beneficial physiological reflexes, which cannot be diminished with impunity except by removal of their underlying causes. When cough is due to irremovable irritation of the bronchioles, such as a neoplasm in the lungs, or excessive irritability of the centre (nervous cough), Opium or Morphine is indicated and gives great relief. On the contrary, when respiratory distress and coughing are associated with abundant mucopurulent expectoration, as in bronchitis, broncho-pneumonia, etc., Opium, by depressing the cough reflex, leads to retention of expectoration and may aggravate dyspnœa or precipitate asphyxia. Between these extremes there are varieties of bronchial and pulmonary conditions in which Opium or Morphine may be used to relieve the discomfort of frequent or fruitless cough, e.g. in bronchial catarrhs, phthisis, etc. The general rule should be to prescribe Opium in small doses along with expectorants, such as Ipecacuanha, Ammonium Bicarbonate, Squill or Volatile Oils; Tinctura Opii Camphorata is a suitable compound preparation, particularly for children. In acute pleurisy or pleuro-pneumonia it may be necessary to relieve severe pain, harassing cough, sleeplessness and mental distress with Morphine hypodermically. In acute pneumonia, Morphine is permissible in the early stages to allay excitement and delirium, but it is contra-indicated later, especially if there is any evidence that the respiratory centre is failing. In hæmoptysis Opium or

Morphine is valuable by inducing quiescence of the patient, slowing respiration and diminishing cough, thus promoting conditions favourable to arrest of the hæmorrhage.

Action on the Spinal Cord.—Morphine and Opium excite the reflex excitability of the spinal cord; this effect is more marked with Opium. All Opium alkaloids possess, in different degree, a strychnine-like action upon the cord. No therapeutic use is made of this action. Morphine has no action upon the sensory or motor nerves or upon voluntary muscle.

Action on the Circulation.—Opium and Morphine have no effects upon the heart or circulatory system. If nausea occurs, the pulse may be accelerated, but otherwise the heart remains uninfluenced until asphyxia from respiratory failure slows the heart and raises blood-pressure. Morphine is, therefore, given in doses above the pharmacopœial maximum to relieve the severe pain of coronary thrombosis or occlusion, but its respiratory effect must be watched.

Diaphoretic Action.—The dilatation of the skin vessels caused by Morphine and Opium is of obscure central origin; it is most marked in the face and neck and produces a sensation of warmth and often perspiration. Opium is used with Ipecacuanha in Dover's Powder to induce free perspiration, lower the temperature and promote sleep at the commencement of febrile attacks or catarrhs; the Ipecacuanha excites perspiration reflexly from gastric irritation, while the Opium appears to act centrally in dilating the vessels. Opium occasionally causes itching and erythematous eruptions in the skin.

Action on Metabolism.—Morphine decreases metabolism partly by reducing movement and partly by depressing respiration; it also diminishes the glycogenic function of the liver and reduces the excretion of sugar in diabetes; its effect is much greater when it is administered by mouth. Opium was used to treat diabetes mellitus but Insulin has now displaced it.

Opium in Obstetrics.—Opium is useful in full doses during the first stage of labour; it usually has little effect on the uterine contractions but, by diminishing anxiety and pain, ensures more satisfactory use of the accessory muscles of parturition. A combination of Morphine and Hyoscine is employed hypodermically as a narcotic during parturition (*see* p. 340). Opium is also serviceable in preventing threatened abortion and to relieve afterpains.

Excretion of Morphine.—The excretion of Morphine commences quickly but it may not be completed for 48 hours because temporary storage takes place in the liver and tissues. It is excreted to about 50 per cent. in the urine; small amounts appear in the saliva, the stomach, and the intestines. Because of its excretion in the stomach, gastric lavage is of value in cases of poisoning. Unexcreted Morphine is destroyed in the liver.

Idiosyncrasy.—Children are unusually susceptible to the action of Opium upon the cerebrum and medulla and it should be given to them only in small doses; at the age of 1 year, 1/2 min. of the Tincture is an adequate dose. Certain persons exhibit idiosyncrasy to Opium and experience vivid nightmares or excitement instead of calm sleep.

Opium Habit.—Opium or Morphine readily causes a drug habit —*morphinism* or *morphomania.* This may take the form of smoking, eating, drinking or injecting hypodermically preparations of Opium or Morphine. It promotes a detached frame of mind, in which the person's business or domestic worries cease to trouble his mind and he indulges in pleasant fanciful dreams; constipation is a prominent symptom. In moderate cases, further effects may not be observed, but most addicts increase the dosage as they become more tolerant, until they neglect business responsibilities, personal cleanliness and moral conventions; emaciation is common from failure to take food. Patients continue the drug mainly from fear of the *withdrawal symptoms,* which consist in a pronounced excitation of the cerebrum, marked by irritable temper, restlessness, possibly delirium and in persistent yawning or sneezing. In addition, vomiting, diarrhœa and pains in the limbs and abdomen are common, and a profound circulatory collapse may occur. The intensity of the craving for the drug is most severe during the first three days following withdrawal.

Treatment consists in sudden or rapid withdrawal of the drug with temporary substitution of another hypnotic, e.g. Hyoscine, Barbitone, Chloral, or Bromides, saline purgatives to remove Morphine excreted into the bowel and hygienic treatment with a prescribed occupation or recreation to absorb the attention.

Action of other Opium Alkaloids.—Of the two chemical groups, the Phenanthrene series—Morphine, Codeine and Thebaine—increase the tone of plain muscle while the Isoquinoline series—Narcotine, Papaverine, etc.—relax the tone and inhibit movement in plain muscle. Morphine, Codeine and Thebaine form a series of descending potency as narcotics and of increasing power as spinal convulsants. Narcotine, Thebaine, Laudanine and

Hydrocotarnine increase reflex excitability, cause restlessness, tremors and finally tetanic convulsions, while Papaverine, Narceine, Protopine and Cryptopine are more purely narcotic, like Morphine. Papaverine has a direct depressant action on involuntary muscle; thus it dilates arterioles, reduces the tone and peristalsis of the intestine and relaxes the bile ducts and the bronchioles.

Papaveretum (B.P.C.), Omnopon, Pantopon—a mixture of the soluble hydrochlorides of Opium alkaloids—is a brown powder containing about 50% Morphine. *Dose.*—By mouth, 10 to 20 mg (1/6 to 1/3 gr.) hypodermically, 5 to 10 mg (1/12 to 1/6 gr.). It is a powerful analgesic and narcotic and used for the general purposes of Morphine in relieving pain and promoting sleep.

Nepenthe.—A proprietary fluid preparation, resembling Tincture of Opium, contains 0·84% of Morphine (about 1/3 gr. in 40 min.). *Dose.*—0·3 to 2·6 Mils (5 to 40 min.).

Codeina.—Codeine. Morphine methyl ester. $C_{17}H_{17}NO(OH)(OCH_3)$, H_2O. An alkaloid obtained from Opium or Morphine.

CHARACTERS.—Colourless crystals; taste bitter; aqueous solutions alkaline. *Solubility.*—1 in 120 of water. *Tests.*—With HNO_3 gives yellow, not red (distinction from morphine); a 2% aqueous solution, acid with HCl, gives no precipitate with dilute ammonia solution (distinction from morphine); a solution in H_2SO_4 with ammonium molybdate or Fe_2Cl_6 gives a deep bluish-violet colour changing to scarlet and orange with HNO_3.

Dose.—Metric, 10 to 60 mg; Imperial, 1/6 to 1 gr.

Codeinæ Phosphas.—Codeine Phosphate. $C_{17}H_{17}NO(OH)(OCH_3)$, H_3PO_4,H_2O.

CHARACTERS.—Colourless, bitter crystals. *Solubility.*—1 in 3·5 of water.

Dose.—Metric, 10 to 60 mg; Imperial, 1/6 to 1 gr.

Preparations

1. **Tabellæ Codeinæ Phosphatis.**—30 mg (1/2 gr.) in each.
2. **Tabellæ Codeinæ Compositæ.**—0·2592 G (4 gr.) of Acetylsalicylic Acid and of Phenacetin, and 8·1 mg (1/8 gr.) of Codeine Phosphate in each.

Dose.—1 or 2 tablets.

ACTIONS AND USES

Codeine has about one-quarter the depressant powers of Morphine upon the sensory area of the cerebrum and is, therefore, less effective in relieving pain or in causing sleep. As a depressant of the respiratory centre and the cough reflex, it is also less active than Morphine but it can influence cough in doses insufficient to relieve pain. Its advantages are that it is less constipating and does not readily cause a habit. In large doses it may cause restlessness and reflex excitability from stimulation of the spinal cord.

Codeine Phosphate is used to relieve mild forms of abdominal pain when it is desired to avoid the constipating effect of Morphine and, in association with expectorants, to relieve troublesome cough.

Diamorphinæ Hydrochloridum.—Diamorphine Hydrochloride. $C_{21}H_{23}NO_5,HCl,H_2O$. Diacetylmorphine Hydrochloride. "Heroin."

SOURCE.—The alkaloid is obtained by acetylation of Morphine.

CHARACTERS.—White crystalline powder; taste bitter. *Solubility.*—1 in 2 of water.

Dose.—Metric 5 to 10 mg; Imperial, 1/12 to 1/6 gr.

ACTIONS AND USES

Diamorphine Hydrochloride **resembles Morphine** in its actions. It is **less depressant** to the sensory area, **less constipating**, but about five times **more depressant to the respiratory centre**, so that respiration is rendered very slow but deep. Diamorphine is used most largely as a respiratory sedative in the irritating cough of laryngitis, bronchitis and pulmonary tuberculosis. Given either by the mouth or hypodermically, it also affords great relief in painful cardiac disease. It readily induces a "habit" resembling that of Morphine, and is used by addicts as a "snuff."

Papaverinæ Hydrochloridum.—Papaverine Hydrochloride. $C_{20}H_{21}O_4N$ HCl. The alkaloid is obtained from Opium or prepared by synthesis.

CHARACTERS.—White crystals or powder, taste slightly bitter. *Solubility.*—1 in 40 of water.

Dose.—Metric, 0·12 to 0·25 G; Imperial, 2 to 4 gr.

ACTIONS AND USES

Papaverine is less analgesic, less toxic and much less narcotic than Morphine. It has a direct depressant action on involuntary muscle; it dilates the arterioles, including the coronary arteries, reduces the tone and peristalsis of the intestine, and relaxes the bronchioles, ureters and bile ducts.

Papaverine is used as a vaso-dilator in angina of effort and in thrombo-angiitis obliterans; and as an analgesic antispasmodic for intestinal colic and during the passage of renal or biliary calculi. In acute asthma, it is used along with Ephedrine. It does not cause a habit

Pethidinæ Hydrochloridum.—Pethidine Hydrochloride. Dolantin. Demerol. The hydrochloride of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate. $C_5H_8N.CH_3.C_6H_5.CO.OC_2H_5,HCl$.

CHARACTERS.—A colourless, crystalline powder, taste bitter; very soluble in water.

Dose.—Metric, 25 to 100 mg; Imperial, 2/5 to 1½ gr.

Preparation

Injectio Pethidinæ Hydrochloridi.—A sterile solution in Water for Injection, labelled with the amount in a suitable dose volume.

Dose.—*Of Pethidine Hydrochloride for subcutaneous injection:* **Metric, 25 to 100 mg; Imperial, 2/5 to 1½ gr.**

ACTIONS AND USES

Pethidine relieves pain less reliably and for a shorter time (2 to 3 hours) than Morphine, but it has the advantages that it relaxes spasm of involuntary muscles and is less depressant to the respiratory centre. Its depressant action on involuntary muscle is partly a direct one and partly due to a depression of the parasympathetic endings. It may cause vaso-dilatation, giddiness, sweating and blurring of vision.

Pethidine is used as a substitute for Morphine in post-operative pain, for pre-medication before general anæsthetics, and during parturition, where it gives a satisfactory analgesia, is said to increase the uterine contractions, and has less depressant action on the infant's respiration than Morphine. For its relaxing action on plain muscle, it is given for intestinal, ureteral and biliary colic and to relieve spasm in asthma. Tolerance can be acquired to Pethidine and habit may be developed.

Amidone Hydrochloride.—Physeptone. Disephonine. Miadone. *dl*-2-dimethylamino-4 : 4-diphenylheptane-5-one hydrochloride.

Dose.—*Orally:* **2·5 to 10 mg (1/24 to 1/6 gr.)**; *intramuscularly or intravenously:* **10 mg (1/6 gr.)**. Available as tablets (5 mg) or ampoules (10 mg in 1 Mil).

ACTIONS AND USES

Disephonine, in similar dose to Morphine, is found to have an equal or greater, although less prolonged (3 to 4 hours) analgesic action, but is less narcotic and less likely to cause nausea, vomiting or habit than Morphine; it is more depressant to the respiratory and cough centres than Pethidine.

Disephonine is used as a substitute for Morphine in relieving pain and cough. For obstetrics, its depressant action on the infant's respiration after birth makes it much less safe than Pethidine.

Phenadoxone.—Heptalgin. Diphenylmorpholinoheptanone hydrochloride.

Dose.—*Orally or by intramuscular injection:* **10 mg (1/6 gr.)**. Available as tablets or ampoules.

ACTIONS AND USES

Phenadoxone is said to be six times more potent as an analgesic than Morphine, and to be less hypnotic and less depressant to the respiratory centre. Given by injection, its action lasts for one to two hours, or given orally, for three to four hours. It also relieves spasm of biliary or ureteral colic.

Cannabis Indica (*not official*).—Indian Hemp. Gunjah. The dried, resinous, flowering or fruiting tops of the pistillate plant Cannabis sativa. N.O. Urticaceæ (grown in India).

COMPOSITION.—An amorphous resin, *cannabinone*, containing a reddish narcotic oil, *cannabinol*, $C_{21}H_{26}O_2$; and *choline*.

Preparation

Tinctura Cannabis Indicæ (B.P.C.).—Extract, 5%; Alcohol 90%.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

ACTIONS AND USES

Cannabis Indica in moderate doses produces **depression of the higher cortical centres**, with impairment of intellect and depression of the perceptive and sensory areas, followed by drowsiness and loss of sense of time and space. In some persons, especially if the drug be smoked and inhaled, there may be pleasing grandiose dreams or hallucinations and purposeless muscular movements or restless delirium. Large doses induce muscular relaxation, numbness of the limbs and diminished perception of touch and pain, ending in deep stuporous sleep. Cannabis has no important actions on the heart or respiration; and does not produce constipation. Usually smoked, it is the basis of the hashish (oriental) marihuana (American) and dagga (S. African) habits.

Cannabis Indica was formerly used as a **hypnotic** and **anodyne**, but owing to its unreliability of action, the drug is now practically abandoned in therapeutics.

ORGANIC HYPNOTICS

A Hypnotic is a drug which produces sleep resembling natural sleep. All depress first the perceptive (consciousness) centres and retard cerebration; in excessive dose they depress the sensory and motor areas, and lastly the spinal cord and medulla. They are here arranged according to their chemical relationships.

ALDEHYDE, ALCOHOL AND KETONE GROUP

Paraldehydum.—Paraldehyde. $(CH_3CHO)_3$.

CHARACTERS.—A colourless liquid; odour unpleasant, ethereal; taste acrid. *Solubility*.—1 in 9 of water; miscible with alcohol 90% and ether.

Dose.—*Orally:*

Metric, 2 to 8 Mils; Imperial, 30 to 120 min.

By rectal injection as a basal anæsthetic:

Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

ACTIONS AND USES

Paraldehyde, being volatile, is rapidly absorbed and induces, in 15 minutes, a light, natural sleep lasting about 6 or 8 hours without causing cardiac or respiratory depression. Patients awake refreshed and are not drowsy. Objections to its use are the unpleasant taste (masked by Tincture of Orange or Cinnamon Water), its excretion in the breath, and its tendency to cause gastric disturbance unless well diluted; occasionally it causes excitement or delirium. Paraldehyde is a safe **hypnotic** for use in asthma, in the insomnia of cardiac and respiratory diseases and in weakly subjects. Habit formation occurs rarely.

Rectal Administration.—A solution of 60 min. per stone body weight in ten times its volume of Normal Saline Solution is employed, particularly for children, as a basal hypnotic; it is given 1½ hours before the operation.

Amyleni Hydras.—Amylene Hydrate Dimethyl-ethyl-carbinol. Tertiary Amyl Alcohol. $(CH_3)_2C_2H_5C.OH$.

CHARACTERS.—A clear, volatile liquid; odour and taste like camphor. *Soluble* in water (1 in 8), freely in alcohol.

Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Amylene Hydrate is a hypnotic intermediate in action between Chloral Hydrate and Paraldehyde. It induces in about 20 minutes sleep which lasts about 6 hours. It tends to cause gastric upset, fall in temperature and mental excitement, but is not very toxic. It is used in Bromethol.

Alcohol Tribromoethylicum.—Tribromoethyl Alcohol, Tribromoethanol. Avertin. CBr_3CH_2OH.

CHARACTERS.—A white crystalline powder, unstable; soluble 1 in 35 of water, easily in Amylene Hydrate.

Preparation

Bromethol.—Fluid Avertin. Solution of Tribromoethyl Alcohol 2, in Amylene Hydrate 1.

Dose.—*By rectal injection as a basal anæsthetic:* (diluted 1 in 39 of Distilled Water at 40° C.). **Metric, 0·075 to 0·1 Mil per Kg; Imperial, 1/2 to 2/3 min. per lb. body weight.**

ACTIONS AND USES

Bromethol is used as a **basal anæsthetic** for slight operations or prior to general anæsthesia. The requisite dose of Bromethol (2·5 to 3 per cent.) in warm water is slowly injected at least 4 in. high in the rectum half an hour before the operation. There is no excitement or discomfort but, in 10 to 15 minutes, respiration becomes slower and shallower and the patient passes into deep narcosis, the face being paler or slightly cyanosed, the pupils small and the eyes fixed. The average period of unconsciousness is from 2 to 4 hours but in only 40 per cent. of cases is an adequate surgical anæsthesia attained; this may be completed by Nitrous Oxide and Oxygen or small amounts of Ether. Bromethol is a relatively safe means of inducing anæsthesia although it lowers blood-pressure and temperature; it is free from post-operative complications; but is contra-indicated in renal disease, as it is excreted slowly by the kidney. It is used for cases of thyrotoxicosis, cardiac and pulmonary disease, for ear, nose and throat operations, for nervous patients, and, as it lowers intracranial pressure, for neuro-surgery.

CHLORAL GROUP—Basal Formula $CCl_3.CH(OH)_2$

Chloralis Hydras.—Chloral Hydrate. Trichloroethylidene glycol. $CCl_3.CH(OH)_2$.

CHARACTERS.—Colourless plates, not deliquescent; odour pungent; taste pungent, rather bitter. *Solubility.*—1 in less than 1 of water. *Incompatibles.*—Alkalis, which liberate chloroform, and alkaline salts (e.g. Barbitonum Sodium).

Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

ACTIONS AND USES

Externally.—Solutions of Chloral Hydrate (1 per cent.) are antiseptic; strong solutions are irritant. Rubbed with equal parts of Camphor or Menthol, it forms a liquid mixture which is used locally as an **anodyne** for neuralgia, chilblains and dental caries.

Internally.—Chloral Hydrate is **irritant** to the stomach and should be given in dilute solution flavoured with Orange. It is absorbed rapidly and circulates as Chloral.

Nervous System.—In therapeutic doses, Chloral Hydrate acts as a **rapid and powerful hypnotic** by depressing the psychical and perceptive centres of the cerebrum; therefore the intellect becomes less active and less responsive to external impressions. It produces, in 15 to 30 minutes, drowsiness, which is followed by natural refreshing sleep lasting from 6 to 8 hours. During slumber the pulse and respiration are slower and the pupils contracted, but the reflexes remain active and pain is not relieved, so that the patient can be roused by sensory stimulation. On waking, the patient may show slight mental confusion, headache or drowsiness. Rarely, brief excitement precedes the hypnotic action.

Large doses (20 to 30 gr.) produce deep prolonged sleep in which, from depression of the cerebral sensory and motor areas and of the spinal cord, pain is dulled and the reflexes are less active. Toxic doses produce a deep coma associated with anæsthesia, abolition of reflexes, muscular relaxation and depression of the medullary centres; the pulse becomes slow and weak, respiration slow and shallow, and death results from paralysis of the respiratory centre.

Circulatory System.—The slowing of the cardiac rate with moderate dosage is seldom greater than that which occurs in natural sleep, but large doses of Chloral Hydrate are direct **depressants to cardiac muscle**, therefore they slow and decrease the force of the heart. Further, by a **depressant action on the vasomotor centre,** Chloral dilates the superficial vessels—shown by flushing of the skin and fall of temperature. These two circulatory effects account for the reduction of blood-pressure produced by Chloral, and are the reasons for its unsuitability as a regular hypnotic in cardiac disease.

Like Chloroform, Chloral Hydrate reduces metabolism by limiting the oxidative processes in the tissues, and its continued use leads to fatty degeneration of the liver, heart, and other internal organs.

Therapeutic Uses.—Chloral Hydrate is suitable as a hypnotic in conditions of mental excitement or anxiety from overwork, distress or hysteria, in the early stages of fevers, or in mild forms of mania and delirium tremens. In such cases it is frequently prescribed along with Bromides. In using Chloral for insomnia in nervous subjects, an endeavour should be made by inculcating regular habits to break its use as early as possible, because such patients become tolerant to Chloral and its frequent use may lead to the establishment of a **drug habit**. For this reason it is not an ideal regular hypnotic.

Its action in reducing the excitability of the motor area and spinal cord led to its use in chorea, eclamptic convulsions, in tetanus and in poisoning from strychnine; its value in these conditions is, however, essentially symptomatic.

Excretion.—Chloral is excreted to a small extent by the lungs but mainly by the kidneys, either as Chloral or as urochloralic acid—a compound of trichloroethyl alcohol and glycuronic acid—which increases the urinary acidity and reduces Fehling's solution but does not ferment. Traces excreted by the skin may account for erythematous eruptions during its use.

Chloral compared with Morphine.—The advantages of Chloral over Morphine are that it acts as a hypnotic more quickly and with greater certainty; after-effects, e.g. headache, sickness, etc., are less frequent; digestive disturbance (if it is freely diluted) and constipation are avoided; and it is safer for children. The disadvantages are that Chloral does not relieve pain, and is less effective in relieving cough and dyspnœa in cardiac and pulmonary disease.

Chlorbutol.—"Chloretone." Chlorobutanol. Trichlor-butyl-alcohol. $CCl_3C(CH_3)_2OH$.

CHARACTERS.—White, crystalline flakes; odour and taste, camphoraceous. *Solubility.*—1 in 125 of water; readily in alcohol: 1 in 33 of liquid paraffin; 1 in 10 of glycerin.
Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

ACTIONS AND USES

Externally.—Chlorbutol is an **antiseptic** and **mild local anæsthetic**. It is used as a powder (10 per cent.) with Chalk and Zinc Oxide or as an ointment to allay irritation in wounds, scalds, pruritus and other skin diseases, and in the form of suppositories for piles. Solutions (1 per cent.) in Liquid Paraffin with antiseptic volatile oils, e.g. Camphor and Menthol 2·5 per cent., are used as paints and sprays in naso-pharyngeal catarrhs and as drops to relieve earache. A saturated solution in Clove Oil is a useful obtundent for sensitive dentine and also allays pain in exposed pulp. It is contained in Liquor Adrenalinæ Hydrochloridi as a preservative.

Internally.—Chlorbutol is slower and less reliable as a hypnotic than Chloral Hydrate, but it does not irritate the stomach nor depress the heart. It may be used in mild cases of nervous insomnia and, because of its local anæsthetic action on the gastric mucosa, it is a valuable remedy for sea-sickness, post-anæsthetic vomiting, hiccough, and the sickness of pregnancy; it is also useful to restrain movements in chorea.

Butylchloralis Hydras (B.P.C.). Butylchloral Hydrate. Trichlorbutylidene glycol. $CH_3.CHCl.CCl_2.CH(OH)_2$.

CHARACTERS.—Pearly-white, flat crystals; odour pungent; taste acrid, nauseous. *Solubility.*—1 in 40 of water, neutral.
Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

ACTIONS AND USES

Butylchloral Hydrate resembles Chloral Hydrate in action. As a **hypnotic** it is less rapid, certain and powerful but somewhat more depressant to the heart than Chloral Hydrate. It is said to be useful in relieving migraine and facial neuralgia.

Chloralformamidum (B.P.C.). — " Chloralamide." $CCl_3CH(OH)NHCHO$.

CHARACTERS.—Colourless, lustrous crystals; odourless; taste slightly bitter. *Solubility.*—1 in 21 of water, neutral. Aqueous solutions decompose at 60° C. into chloral hydrate and formamide.
Dose.—Metric, 1 to 3 G; Imperial, 15 to 45 gr.

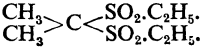
ACTIONS AND USES

Chloralamide is a *hypnotic*, and produces, in about an hour, sleep which lasts for 6 to 8 hours. It is slower in action than Chloral Hydrate, but produces no effect on the circulation except in toxic doses. It is decomposed in the body into Chloral Hydrate and ammonium formate. It is a mild and safe hypnotic, especially in cardiac and nervous diseases and alcoholism. It is also used to prevent sea-sickness and train-sickness. It does not readily induce a "habit." It is excreted as urochloralic acid, but only slowly, hence cumulation may occur.

SULPHONE GROUP

The action of these hypnotics depends on the presence of alkyl radicals (methyl, ethyl, etc.) united to the disulphone group. The ethyl radical is more powerfully hypnotic than that of methyl; therefore the action becomes stronger as the number of ethyl radicals increases.

Sulphonal.—Diethyl-sulphone-dimethyl-methane.



$$\begin{matrix} CH_3 \\ CH_3 \end{matrix} > C < \begin{matrix} SO_2.C_2H_5. \\ SO_2.C_2H_5. \end{matrix}$$

CHARACTERS.—Colourless, prismatic crystals; odourless and nearly tasteless; neutral. *Solubility.*—1 in 450 of cold, 1 in 15 of boiling, water.
Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

ACTIONS AND USES

Sulphonal is tasteless and almost insoluble, therefore, although it does not disturb digestion, it is **very slowly absorbed**. It **requires 4 to 5 hours to induce sleep**, which lasts some 10 to 12 hours and is accompanied by normal slowing of the pulse and respiration.

On waking, the patient is refreshed but feels drowsy and lethargic, because Sulphonal is very slowly excreted during a day or two after administration, and therefore regular use will lead to accumulation in the tissues. For this reason Sulphonal is employed rarely except in mental diseases. It does not relieve pain.

Large doses in weakly persons or repeated dosage give rise to **symptoms of cumulation**: these are headache, mental dullness and confusion, along with abdominal pain, sickness and diarrhœa, muscular weakness or cramps and pareses; urticarial skin rashes are also common. The appearance of a deep cherry colour and the spectrum of **hæmatoporphyrin** in the urine, due to decomposition of hæmoglobin, is an indication of serious poisoning. Because of these actions and the danger of a Sulphonal habit, the drug must be ordered with forethought. Sulphonal is excreted chiefly unchanged, but partly as ethyl-sulphonic acid, in the urine.

Methylsulphonal (B.P.C.).—Diethyl-sulphone-methyl-ethyl-methane. Trional.

Dose.—Metric 0·3 to 1·2 G; Imperial, 5 to 20 gr.

ACTIONS AND USES

Methylsulphonal is a more **powerful and rapid hypnotic** than Sulphonal, and induces sleep in from 30 to 60 minutes. The sleep lasts for about 8 or 10 hours and there is less marked drowsiness on the following day. It may induce the same toxic symptoms as Sulphonal. It is usually given in cachets to treat mental diseases.

UREA GROUP

These are derivatives of urea $\mathrm{OC}<\genfrac{}{}{0pt}{}{\mathrm{NH_2}}{\mathrm{NH_2}}$ or carbamic acid $\mathrm{OC}<\genfrac{}{}{0pt}{}{\mathrm{NH_2}}{\mathrm{OH}}$ The hypnotic powers of these Ureides vary with the number of alkyl radicals they contain.

Urethanum.—Urethane. Ethyl Carbamate. $\mathrm{OC}<\genfrac{}{}{0pt}{}{\mathrm{NH_2}}{\mathrm{OC_2H_5}}$.

CHARACTERS.—White crystals; odourless; taste cool, saline, slightly bitter; easily *soluble* in water.

Dose.—Metric, 1 to 2 G; Imperial, 15 to 30 gr.

ACTIONS AND USES

Urethane is a **mild** but **unreliable hypnotic** which may produce calm sleep in from 20 to 30 minutes. It does not depress the heart or respiration, and is excreted as urea, which acts as a diuretic. Urethane is useful as a hypnotic mainly for children.

Urethane, in doses of 0·6 to 5 G (8 to 75 gr.) daily, has proved useful in the treatment of chronic myeloid leukæmia; Urethane inhibits the proliferation of lymphocytes and to a lesser extent of granulocytes; it may lower the lymphocyte count to normal in two to four weeks and reduce the size of the lymph nodules and spleen, with consequent improvement in health and a longer survival period. Less satisfactory improvement occurs in lymphatic leukæmia while acute leukæmia is hardly influenced. If the large doses cause nausea, rectal administration is used.

Carbromalum (B.P.C.).—Carbromal. Uradal. Adalin. Bromo-ethyl-butyryl-carbamide. $H_2N.OC.NH.CO.CBr(C_2H_5)_2$. A white, crystalline, insoluble powder.

Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

ACTIONS AND USES

Carbromal is a useful sedative and **mild hypnotic**, acting in 30 minutes and producing no after-effects. It is used in insomnia of nervous origin, and in the restlessness of cardiac and mental diseases.

Bromvaletonum (B.P.C.).—Bromural. Dormigene. Monobrom-iso-valerianyl-urea.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

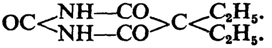
Bromvaletone induces sleep in half an hour, and is a useful **mild hypnotic** in neuroses where there is no pain, cough, fever or excitement. Its action lasts about 4 hours.

BARBITURIC ACID SERIES

These are derivatives of barbituric acid or malonyl urea, the character and length of their hypnotic actions being dependent upon (*a*) their speed of absorption, (*b*) their rate of excretion by the urine, (*c*) their rate of detoxication by the tissues, mainly by the liver, and (*d*) the constitution of the side chains. Those with longer side chains are usually more rapidly destroyed and have shorter actions. They are subdivided into groups in accordance with their length of hypnotic action.

1. Long-acting Barbiturates.—These take from half to one hour to induce sleep which lasts 10 or 12 hours and there may be after-drowsiness; little is destroyed by the liver, most is excreted in the urine in twelve hours.

Barbitonum.—Barbitone. Barbital. Veronal. Diethyl-barbituric Acid.



$$\mathrm{OC}<^{\mathrm{NH-CO}}_{\mathrm{NH-CO}}>\mathrm{C}<^{\mathrm{C_2H_5.}}_{\mathrm{C_2H_5.}}$$

CHARACTERS.—A white, crystalline powder; odourless; taste bitter. *Solubility.*—1 in 170 of water; more soluble in hot water, in alcohol 90% and in alkalis. Boiled with NaOH, evolves ammonia.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparation

Tabellæ Barbitoni.—*Dose* of Barbitone, 0·3 to 0·6 G (5 to 10 gr.).

Barbitonum Sodium.—Soluble Barbitone. Barbital Sodium. Medinal. The monosodium salt of diethyl-barbituric acid.

CHARACTERS.—A white, crystalline powder. *Solubility.*—1 in 6 of water.
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparation

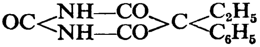
Tabellæ Barbitoni Sodii.—*Dose* of Barbitone Sodium, 0·3 to 0·6 G (5 to 10 gr.).

ACTIONS AND USES

Barbitone is a **powerful hypnotic**, inducing within half to one hour quiet, dreamless and refreshing sleep, which lasts 8 to 10 or more hours; Soluble Barbitone acts more rapidly. Barbitone causes no disturbance of digestion; the heart, vascular system, respiration, kidneys and body temperature are uninfluenced by therapeutic doses; and there are no after-effects, except lethargy. Therapeutic doses do not relieve pain. Tolerance is not readily acquired and therefore an increase of dosage is not usually necessary; the drug is excreted mainly unchanged in the urine during about four days but cumulation is not common. In some persons, erythematous or purpuric skin eruptions occur. A drug habit may, however, easily become established and lead to over-dosage, which produces symptoms of mental confusion, dementia, ataxic movements and, finally, from depression of the medulla, respiratory failure, preceded by pulmonary œdema or pneumonia.

Barbitone has been found specially useful in the insomnia of neurasthenia, cardiac disease, fever, irritating cough, mental disorder, morphinism and alcoholism. It is also valuable in half its hypnotic dosage as a sedative in cases of chorea, thyrotoxicosis and in sea-sickness and the vomiting of pregnancy. Full doses are necessary to control mania and delirium tremens and, in difficult cases, Soluble Barbitone may be injected hypodermically.

Phenobarbitonum.—Phenobarbitone. Phenobarbital. Gardenal. Luminal. Phenyl-ethyl barbituric acid.



$$\mathrm{OC}{<}\begin{matrix}\mathrm{NH{-}CO}\\\mathrm{NH{-}CO}\end{matrix}{>}\mathrm{C}{<}\begin{matrix}\mathrm{C_2H_5}\\\mathrm{C_6H_5}\end{matrix}$$

CHARACTERS.—A white, crystalline powder; odourless, taste bitter. *Solubility.*—1 in 1000 of water; soluble in alcohol 90% and in alkalis.
Dose.—Metric, 30 to 120 mg; Imperial, 1/2 to 2 gr.

Preparation

Tabellæ Phenobarbitoni.—*Dose* of Phenobarbitone, 30 to 120 mg (1/2 to 2 gr.).

Phenobarbitonum Sodium.—Soluble Phenobarbitone. Phenobarbitone Sodium. The monosodium salt of phenyl-ethyl barbituric acid.

CHARACTERS.—A white, hygroscopic powder; odourless; taste bitter. *Solubility.*—Readily in water.

Dose.—*Orally:*

Metric, 30 to 120 mg; Imperial, 1/2 to 2 gr.

Single dose by intravenous or intramuscular injection:

Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

Preparations

1. **Injectio Phenobarbitoni Sodii.**—A sterile solution in Water for Injection free from CO_2, and in sealed containers labelled with the amount.

Dose.—*Single, by intravenous or intramuscular injection:*

Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

2. **Tabellæ Phenobarbitoni Sodii.**—*Dose* of Phenobarbitone Sodium, 30 to 120 mg (1/2 to 2 gr.).

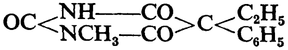
ACTIONS AND USES

Phenobarbitone and its soluble Sodium salt, which acts more quickly, are more slowly excreted than Barbitone and have a **more prolonged** (10 to 12 hours) action which is **more sedative than hypnotic**. They depress the motor area particularly and to a less degree the sensory area. They are liable to cause amnesia and, when used as mental sedatives at night, patients may forget having taken a previous dose or doses, with serious results; no more than two tablets should be permitted at the bedside.

As motor sedatives, small doses have a lengthy effect in allaying excitement in nervous or thyrotoxic subjects, and are also given half an hour before minor operations or local anæsthetics to decrease apprehension and thus to reduce Adrenaline formation. As sensory sedatives, they relieve neuralgia and migraine but not acute pain.

Larger doses, by depression of the motor cortex, are valuable sedatives in **epilepsy**; they reduce the severity and frequency of the fits but cause less intellectual depression or drowsiness than Bromides and do not produce acne. Gradual reduction of the controlling dose is advisable to obviate status epilepticus. Phenobarbitone is useful also to diminish spasms or convulsive movements in chorea, eclampsia, status epilepticus and tetanus; in urgent cases the Sodium salt may be injected. Phenobarbitone has a smaller safety margin than Barbitone, skin rashes are more common and it should be avoided in renal or cardiac diseases.

Methylphenobarbitonum.—Methylphenobarbitone. Phemitone. Prominal. N-methyl-5-phenyl-5-ethyl barbituric acid.



$$\mathrm{OC}<\begin{array}{l}\mathrm{NH{-}{-}CO}\\ \mathrm{NCH_3{-}CO}\end{array}>\mathrm{C}<\begin{array}{l}\mathrm{C_2H_5}\\ \mathrm{C_6H_5}\end{array}$$

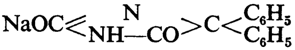
CHARACTERS.—A white, crystalline powder; almost insoluble in water.

Dose.—Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

ACTIONS AND USES

Methylphenobarbitone is more powerfully depressant to the motor cortex, but less hypnotic than Phenobarbitone. It is used in the treatment of **epilepsy** and controls both petit and grand mal seizures without seriously impairing mentality. It is also used in other motor spasmodic conditions and in migraine, like Phenobarbitone.

Phenytoinum Sodium.—Soluble Phenytoin. Epanutin. Solantoin. Sodium diphenylhydantoinate.



$$\mathrm{NaOC}\lll\begin{array}{l}\mathrm{N}\\ \mathrm{NH{-}CO}\end{array}>\mathrm{C}<\begin{array}{l}\mathrm{C_6H_5}\\ \mathrm{C_6H_5}\end{array}$$

CHARACTERS.—A white, hygroscopic powder, absorbing CO_2 and liberating diphenylhydantoin; soluble in water.

Dose.—Metric, 50 to 100 mg; Imperial, 3/4 to $1\frac{1}{2}$ gr.

ACTIONS AND USES

Phenytoin is chemically and pharmacologically related to barbiturates. It reduces the number and severity of grand mal fits in epileptics more effectively than it controls petit mal, and is much less hypnotic and mentally depressing than Phenobarbitone. As it is highly alkaline, it can cause gastric upset unless taken in weak aqueous solution; it is liable to produce toxic effects such as gingivitis and hyperplasia of the gums, giddiness, skin rashes, sometimes purpuric or exfoliative, as well as tremors, ataxia and ptosis, and occasionally mental confusion.

Troxidone.—Tridione. 3 : 5 : 5-trimethyl-oxazolidine-2 : 4-dione.

Dose.—1 to 2 G (15 to 30 gr.) per day in divided doses.

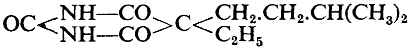
USES

Tridione is very effective in resistant cases of petit mal and in controlling status epilepticus, but is ineffective for grand mal seizures. As it is liable to cause photophobia, dermatitis and agranulocytosis, it should be used only if other drugs fail and stopped if toxic symptoms appear. Although not a barbiturate, it is inserted here with other drugs controlling epilepsy.

Proponal.—Dipropylbarbituric Acid. *Dose.*—0·12 to 0·5 G (2 to 8 gr.). Proponal, which is more powerful than Barbitone and has a smaller safety margin, is sometimes used for mental cases.

2. Intermediate-acting Barbiturates.—Their hypnotic action begins in about half an hour and lasts six to eight hours.

Amylobarbitonum (B.P.C.).—Amylobarbitone. Amytal. 5-isoamyl-5-ethylbarbituric acid.



$$OC<\begin{matrix}NH-CO\\NH-CO\end{matrix}>C<\begin{matrix}CH_2.CH_2.CH(CH_3)_2\\C_2H_5\end{matrix}$$

CHARACTERS.—A white, crystalline, insoluble powder, taste bitter.
Dose.—*Hypnotic:*
Metric, 0·1 to 0·3 G; Imperial, 1½ to 5 gr.

Amylobarbitonum Sodium (B.P.C.).

CHARACTERS.—A white, granular, soluble powder, taste bitter.
Dose.—*Orally, anæsthetic:*
Metric, 0·2 to 0·6 G; Imperial, 3 to 10 gr.
By intravenous injection:
Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

ACTIONS AND USES

Amylobarbitone and its Sodium salt are quickly absorbed and soon detoxicated, little is excreted; they act in the hypnotic dosage in half an hour and sleep lasts 6 or 8 hours with no after-drowsiness, but they are less useful, because shorter acting, as sedatives for nervous patients than Phenobarbitone.

They have also been used as pre-anæsthetic or basal narcotics, given orally, or *per rectum* in 3 per cent. solution, one hour before operations, or intravenously as the Sodium salt in 10 per cent. solution injected very slowly, which acts in five minutes.

Unconsciousness lasts 6 or more hours and the patient is drowsy for about a day. For surgical anæsthesia, Nitrous Oxide with Oxygen or Ether are necessary as supplements, but the Amylobarbitone reduces the amounts of these required.

Allobarbitonum (B.P.C.).—Dial. 5 : 5-diallylbarbituric acid.

CHARACTERS.—A white, slightly soluble and bitter crystalline powder.
Dose.—Metric, 30 to 200 mg; Imperial, 1/2 to 3 gr.

ACTIONS AND USES

Allobarbitone acts more quickly than Barbitone, but is more rapidly excreted and thus has a shorter hypnotic action; it is given in tablets and is a fairly safe and satisfactory hypnotic.

Butobarbitonum (B.P.C.).—Butobarbitone. Soneryl. Neonal. 5-*n*-butyl-5-ethylbarbituric acid.

CHARACTERS.—A white, crystalline, slightly soluble and bitter powder.
Dose.—Metric, 60 to 120 mg; Imperial, 1 to 2 gr.

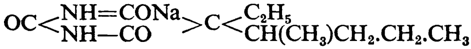
ACTIONS AND USES

Butobarbitone has a more powerful action than Barbitone, hence its smaller dosage; it acts more quickly, in about half an hour, is a good hypnotic and mild analgesic, but, being rapidly destroyed, its action is less prolonged, hence it causes no lassitude the following day.

Other barbiturate hypnotics which have the intermediate type of action are *Ipral*, ethyl-isopropylbarbituric acid. *Dose.*—0·12 to 0·25 G (1/5 to 2/5 gr.); *Alurate*, allyl-isopropylbarbituric acid. *Dose.*—60 to 120 mg (1 to 2 gr.); *Sandoptal*, allyl-isobutylbarbituric acid. *Dose.*—0·2 to 0·8 G (3 to 12 gr.); and *Nostal*, isopropyl-bromallylbarbituric acid. *Dose.*—0·1 to 0·3 G (1½ to 5 gr.)

3. Short-acting Barbiturates.—These act as hypnotics in from a quarter to half an hour and sleep lasts about four to six hours with no after-drowsiness.

Pentobarbitonum Sodium.—Soluble Pentobarbitone. Pentobarbital Sodium. Nembutal. The monosodium salt of 5-ethyl-5-(1-methylbutyl)-barbituric acid.



$$OC{<}\begin{matrix}NH{=}CONa\\NH{-}CO\end{matrix}{>}C{<}\begin{matrix}C_2H_5\\CH(CH_3)CH_2.CH_2.CH_3\end{matrix}$$

CHARACTERS.—A white, crystalline, soluble, slightly bitter powder.
Dose.—Metric, 0·1 to 0·2 G; Imperial, 1½ to 3 gr.

ACTIONS AND USES

Pentobarbitone may be used as a rapid but short-acting hypnotic for patients who have difficulty in going to sleep; it is rapidly detoxicated in the liver, hence its action lasts about 4 to 6 hours only.

It is used mostly as a pre-anæsthetic, amnesic hypnotic or basal anæsthetic, given either orally, or *per rectum* as a suppository, about an hour before operation or childbirth; or it may be given orally the night before and again on the morning of the operation. Unconsciousness lasts from 3 to 6 hours and anæsthesia can then be completed by lesser amounts of Nitrous Oxide with Oxygen, or Ether, than usual. Pentobarbitone is safer than Amylobarbitone; its effects do not last so long and there is less after-drowsiness, but its depressant action on the respiratory centre in anæsthetic dosage must be remembered.

In childbirth as an amnesic and analgesic agent, Pentobarbitone 0·2 G (3 gr.) with Chloral Hydrate 2 G (30 gr.) is given well diluted in lemonade when the pains are regular and the os uteri half dilated, and about half this dose repeated three hours later if labour is protracted.

Pentobarbitone may also be given intravenously in doses of 0·2 to 0·5 G (3 to 8 gr.) in 10 Mils (150 min.) of Water for Injection to alleviate the convulsions in strychnine poisoning and tetanus, or in maniacal excitement.

Pernocton.—Sodium butyl-bromallyl barbiturate.

CHARACTERS.—A white, crystalline powder; taste bitter; *soluble* in water.

Dose.—*Intravenously:* **1 to 3 Mils (15 to 45 min.) of a 10% solution.**

ACTIONS AND USES

Pernocton is less safe than Nembutal and the unconsciousness lasts from 4 to 6 hours. The injection should be given slowly about 15 minutes before operation and stopped if the patient falls asleep. It is used as a *basal hypnotic* prior to general anæsthetics and in obstetric practice. It may be given intramuscularly in doses of 1 to 2 Mils of a 10 per cent. solution.

Cyclobarbitonum (B.P.C.).—Cyclobarbitone. Phanodorm. Phanodorn. 5-ethyl-5-$\triangle^1$-*cyclo*hexenylbarbituric acid.

CHARACTERS.—A colourless, crystalline, slightly soluble and bitter powder.

Dose.—Metric, 0·2 to 0·4 G; Imperial, 3 to 6 gr.

ACTIONS AND USES

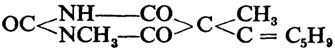
Cyclobarbitone is quickly absorbed and rapidly excreted, hence its effects are of short duration. It is used for patients who have difficulty in commencing to sleep and for nervous insomnia.

Quinal Barbitone Sodium.—Seconal. Sodium methylpropyl-carbonyl-allyl barbiturate. *Dose.—Hypnotic:* 0·1 to 0·2 G (1½ to 3 gr.); *pre-anæsthetic:* 0·2 to 0·3 G (3 to 5 gr.) acts rapidly but its duration is short.

Hebaral Sodium.—Ortal, Ethyl-*n*-hexylbarbituric acid. *Dose.*—Metric, 0·2 to 0·4 G; Imperial, 3 to 6 gr. This also acts rapidly, is excreted quickly and has a short action of about 4 to 6 hours. It is used for initial sleeplessness and pre-operation apprehension.

4. Very Short-acting Barbiturates.—When used as hypnotics, these act in about 15 minutes but they are rapidly detoxicated and sleep will last for only 2 or 3 hours.

Hexobarbitonum.—Hexobarbitone. Evipan. 5-Δ^1-*cyclo*hexenyl-5-methyl-N-methylbarbituric acid.



$$OC{<}\begin{matrix}NH\text{——}CO\\NCH_3\text{—}CO\end{matrix}{>}C{<}\begin{matrix}CH_3\\C = C_5H_9\end{matrix}$$

CHARACTERS.—Colourless, prismatic crystals, tasteless, almost insoluble.
Dose.—*Orally:* **Metric, 0·25 to 0·5 G; Imperial, 4 to 8 gr.**

Hexobarbitonum Sodium.—Hexobarbitone Sodium. Soluble Hexobarbitone. Evipan Sodium.

CHARACTERS.—A white, very hygroscopic, soluble powder, taste bitter.
Dose.—*By intravenous or intramuscular injection:*
Metric, 0·2 to 1 G; Imperial, 3 to 15 gr.
By rectal injection:
Metric, 2 to 4 G; Imperial, 30 to 60 gr.

Preparation

Injectio Hexobarbitoni Sodii.—A sterile solution made by dissolving the contents of a sealed container immediately before use in the required amount of Water for Injection, free from CO_2.
Dose.—*Of Hexobarbitone Sodium by intravenous or intramuscular injection:*
Metric, 0·2 to 1 G; Imperial, 3 to 15 gr.

ACTIONS AND USES

Given orally, Hexobarbitone is rapidly absorbed and has a short intensive action; sleep is induced in 10 minutes and passes into natural sleep; excretion is rapid and after-effects absent.

Hexobarbitone Sodium in solution is injected into a vein of the arm. It is a rapid anæsthetic but, as it is quickly detoxicated by the liver, the action is brief. It produces, in 15 to 25 seconds, unconsciousness accompanied by a deep yawn and slowing of respiration; the jaw drops, hence a prop should be inserted previously and provision made to ensure and maintain unobstructed breathing, if necessary, by the use of an oral airway. The blood-pressure falls, often by about 20 per cent., hence the recumbent posture is necessary; muscular twitchings of the arm and face are often seen and the reflexes are not completely abolished; the pupils are dilated, the corneal reflex is absent but the light reflex is usually present. Recovery is rapid but the speed depends upon the dosage. After effects, e.g. headache, are not very common, but fatal respiratory failure has occurred in a few cases.

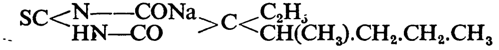
Technique.—Injection at the rate of 1 Mil in 5 seconds is made of 2 to 3 Mils of a 10 per cent. solution; a "safety pause" is made for 30 seconds and (*a*) if unconsciousness follows, this will last for 2 to 3 minutes and suffice for abscess incisions, simple extractions of teeth, etc.; the patient recovers rapidly and, after recumbency for 30 minutes, may be fit to be taken home; (*b*) if unconsciousness is not lost, 2 or 3 Mils more are injected; anæsthesia should then last 5 to 10 minutes; for longer operations, 5 to 7 Mils are given without a break; unconsciousness then lasts from 10 to 20 minutes, and at least an hour's recumbency must be allowed for recovery.

For rectal use, 0·2 Mil (3 mins.) per lb. body weight of a 10 per cent. aqueous solution is given two hours after an enema of Sodium Bicarbonate and one hour after an injection of Morphine.

Precautions.—It should not be administered single-handed, nor in the upright position, nor to old or feeble persons, nor to those with impaired liver function; the respiration must be carefully watched and respiratory stimulants kept at hand. Often the anæsthesia has to be supplemented by Nitrous Oxide and Oxygen.

Uses.—Hexobarbitone Sodium is considered to be a convenient anæsthetic for short surgical and dental operations as it can be given in a home or hospital bed, and because there is little hæmorrhage owing to the lowered blood-pressure. It is also used to induce rapidly an anæsthesia which is to be maintained by Nitrous Oxide with Oxygen, Ether, or other inhalation anæsthetic.

Thiopentonum Sodium.—Thiopentone Sodium. Thiopental Sodium. Pentothal. A mixture of 100 parts of the monosodium derivative of 5-ethyl-5-(1-methylbutyl)-thiobarbituric acid with 6 parts of Exsiccated Sodium Carbonate as buffer.



$$\mathrm{SC}{<}\substack{\mathrm{N\text{——}CONa} \\ \mathrm{HN\text{—}CO}}{>}\mathrm{C}{<}\substack{\mathrm{C_2H_5} \\ \mathrm{CH(CH_3).CH_2.CH_2.CH_3}}$$

CHARACTERS.—A yellowish-white, hygroscopic, soluble powder; odour alliaceous, taste bitter.

Dose.—*By intravenous injection:*

Metric, 0·1 to 0·5 G; Imperial, $1\frac{1}{2}$ to 8 gr.

Preparation

Injectio Thiopentoni Sodii.—A sterile solution made by dissolving the contents of a sealed container in the required amount of Water for Injection immediately before use.

Dose.—*Of Thiopentone Sodium by intravenous injection:*

Metric, 0·1 to 0·5 G; Imperial, 1½ to 8 gr.

ACTIONS AND USES

Thiopentone Sodium is a **rapidly-acting** and **powerful anæsthetic** resembling Hexobarbitone in its actions and effects. The chief advantages of the intravenous barbiturates are that induction is speedy and quiet with no excitement, struggling, holding of the breath or respiratory irritation. Thiopentone is quickly detoxicated by the liver. Under its influence the pupils are dilated, the corneal reflex absent but the light reflex present, and the body reflexes are not completely abolished.

Thiopentone Sodium is given intravenously in 5 or 2·5 per cent. solutions prepared immediately before use and is injected at the rate of 1 Mil in 15 seconds, care being taken that none escapes the vein as it is irritant and may cause necrosis: strengths over 5 per cent. would cause sclerosis of the vein.

The initial dose, when using a 5 per cent. solution in a 10-Mil syringe, is commonly 2 to 3 Mils (0·1 to 0·15 G.). Unconsciousness and relaxation occur in 30 seconds, the jaw drops, respiration becomes shallow, and the blood-pressure falls, therefore the patient should be recumbent. After a short pause to estimate the patient's reaction, the remaining 8 or 7 Mils in the syringe are injected, the anæsthesia will then last about 15 to 20 minutes; but if longer anæsthesia is necessary, additional doses of 1 to 2 Mils (0·05 to 0·1 G) given every five or more minutes will maintain anæsthesia, the indications for further doses being deepening respirations, rising pulse rate and movements of the hands or facial muscles. For children, and aged or debilitated patients, it is desirable to use a 2·5 per cent. solution, giving the same number of Mils and avoiding, if possible, a total dose of more than 0·25 G; special care should be used in cases with myocardial disease. For thoracic surgery, a dose of 0·5 G with additional doses of 0·25 G may be required.

Consciousness will return from a small dose within five or ten minutes, but complete recovery, depending on the total dosage—which should rarely exceed 1·5 G—may take an hour or more, during which the patient should be recumbent; post-operative vomiting is rare. Thiopentone is a safer and less prolonged anæsthetic than Hexobarbitone, but respiratory failure may occur, therefore analeptics such as Picrotoxin, Nikethamide or Leptazol should be available. Laryngeal spasm may happen but can be averted or treated by Atropine.

Thiopentone Sodium is valuable for minor or dental operations, *for setting of fractures, for nose and throat operations, for patients* with respiratory disease, in thoracic surgery, and for neurosurgery as it reduces intracranial pressure. It is also used largely to induce anæsthesia rapidly before giving an inhalation anæsthetic such as Nitrous Oxide or Cyclopropane with Oxygen, or Ether. Thiopentone is employed very frequently in conjunction with *d*-Tubocurarine Chloride (*see* p. 321) which completes the muscular relaxation, but the two solutions must be given separately. Thiopentone by rectal injection (0·04 G per Kg. body weight) has no special advantages, except for children (0·1 G per year) when it gives a satisfactory brief sedation.

Thialpentone.—Kemithal. Sodium 5-Δ^2-cyclohexenyl-5-allyl-2-thiobarbiturate. Available (10 per cent.) in ampoules. It is given in 5 or 10 per cent. solution in water in doses of 0·75 to 1·5 G. as an intravenous anæsthetic, adding 0·1 G. when required. It is equally effective to Thiopentone and less depressant to respiration.

DRUGS ACTING ON GANGLIA

The drugs which act upon ganglionic cell stations produce (*a*) *stimulation*, e.g. small doses of Nicotine, Coniine, Lobeline, Gelseminine, Cytisine and Sparteine, or (*b*) *depression*, e.g. large doses of these alkaloids and also Curarine (Tubocurarine). Nicotine, Coniine, etc., briefly stimulate and then depress. Curarine only depresses. Tetraethyl-ammonium bromide (*see* p. 254) blocks autonomic ganglia.

Nicotine (*not official*).—$C_{10}H_{14}N_2$. A liquid alkaloid obtained from Tobacco. It *stimulates and then paralyses the excitor cells or receptors of all autonomic ganglia.* Thus it causes at first slowing of the pulse, raises the blood-pressure rapidly and greatly by vaso-constriction from stimulation of the splanchnic ganglia, increases the movements of plain muscle—including the intestine—and increases glandular secretions. Larger doses accelerate the heart by paralysis of the vagal ganglia and stimulation of the accelerator mechanism, lower blood-pressure by paralysing the sympathetic ganglia, check peristalsis and glandular secretions, and relax the muscles of the bronchioles. On voluntary motor endings, Nicotine first stimulates the muscle receptors or excitor cells, but later it has a curarine-like effect. Nicotine is not used in therapeutics. Excessive use of **Tobacco** may lead to weakness and arrhythmia of the heart, gastro-intestinal disturbances, cough from irritation of the throat and bronchi; and partial blindness, tobacco amblyopia (central scotoma), from a toxic neuritis.

Coniine (*not official*).—$C_5H_9(C_3H_7)NH$. A liquid alkaloid from Conium maculatum, the Spotted Hemlock. N.O. Umbelliferæ.

Coniine paralyses the myoneural junctions in voluntary muscles, like Curarine, and, therefore, causes ascending motor paralysis. It also at first stimulates and later depresses autonomic ganglia. Death follows paralysis of the phrenic nerve endings. Coniine preparations have been used in chorea and other spasmodic conditions with little or no benefit.

Spartein (*not official*).—$C_{15}H_{26}N_2$. A liquid alkaloid obtained from Sarothamnus scoparius, Broom, N.O. Leguminosæ.

Sparteine Sulphate (*Dose*, 1 to 2 gr.) acts like Coniine both on ganglia and voluntary myoneural junctions. In small doses its only effect is to slow and weaken the cardiac systoles. It has no therapeutic value.

Lobeline is discussed on p. 268.

Gelsemii Radix (*not official*).—Yellow Jasmine. The dried rhizome and roots of Gelsemium sempervirens, N.O. Loganiaceæ. It contains two alkaloids, *gelseminine*, acting like Coniine, and *gelsemine*, acting like Strychnine.

Gelsemium owes its action to gelseminine, which stimulates and then paralyses ganglia and in large doses paralyses voluntary nerve-endings. It is also a cerebral and medullary depressant. Gelsemium is credited with a specific depressant action on the fifth nerve, and Tinctura Gelsemii (5 to 15 min.) has been used in sick headache (migraine) and trigeminal neuralgia, occasionally with success.

PERIPHERAL VOLUNTARY MOTOR DEPRESSANTS

Tubocurarinæ Chloridum (B.P.C.).—*d*-Tubocurarine Chloride. Curarine. $C_{38}H_{44}O_6N_2Cl_2,5H_2O$. The chloride of the alkaloid, *d*-tubocurarine, obtained from Chondrodendron tomentosum or similar species. N.O. Menispermaceæ.

CHARACTERS.—A white, crystalline powder, sparingly soluble in water. *Test:* A saturated aqueous solution gives with a few drops of Fe_2Cl_6 a green colour becoming brown on warming.

Dose.—Determined by the physician in accordance with the needs of the patient.

ACTIONS AND USES

Tubocurarine paralyses voluntary muscles by preventing the chemical mediator, acetylcholine, formed at the myoneural junctions, from influencing the muscle receptor. Possibly the acetylcholine has to pass through a semi-permeable membrane to reach the muscle receptor, and Tubocurarine may retard or prevent the passage through this membrane of the acetylcholine, thus affording time for hydrolysis of it by cholinesterase so that insufficient acetylcholine to excite contraction reaches the muscle receptors.

The only important action of Tubocurarine in clinical dosage is weakness and then paralysis of the voluntary muscles; this begins in the eyes, face and neck, and extends rapidly to the limbs, abdomen, intercostal muscles and lastly the diaphragm; recovery occurs in the reverse order. Tubocurarine is injected intravenously. The maximal effect is developed in 2 or 3 minutes and becomes less intense after 20 to 30 minutes; small increments only, after the initial dose, are required to maintain the effect. Tubocurarine does not affect the heart, liver, kidneys or other organs; it may cause ropy salivation but this is obviated by giving Atropine.

Technique.—After thorough investigation of the patient, light pre-medication with Morphine 10 mg (1/6 gr.) and Atropine 0·4 mg (1/150 gr.) is given an hour before operation. The solution of Tubocurarine is usually 10 mg (1/6 gr.) in 1 Mil of Water for Injection. An initial test dose of 5 mg (1/12 gr.) of Tubocurarine is given intravenously while the patient is still conscious and its effects watched for 2 minutes; usually this causes only drowsiness and heaviness of the eyelids which often close, but no ptosis. If complete ptosis, speech, or respiratory difficulty occurs, the patient is hypersensitive. If after 2 minutes no unusual reaction arises, a further dose of 10 mg (1/6 gr.) is given and followed immediately by 0·5 G (8 gr.) of Thiopentone Sodium intravenously. As Thiopentone acts in a few seconds while Tubocurarine's action is maximal in 2 minutes, the full effect of both drugs is thus simultaneous. If desired, Tubocurarine in a form miscible with Thiopentone solution may be used. An endotracheal tube or pharyngeal airway is introduced and connected with a closed-circuit anæsthetic apparatus. Further anæsthesia is maintained, when necessary, by Thiopentone, by Nitrous Oxide with Oxygen, by Cyclopropane in aged or cardiac cases, or by Ether in small amounts, as Ether itself has a curarine-like action.

Increments of Tubocurarine are given, when necessary, to maintain the degree of muscular relaxation in doses of 2 to 5 mg (1/30 to 1/12 gr.) at intervals of about 25 minutes; a total dose of 45 mg. (2/3 gr.) should not be exceeded.

Means for assisting respiration must be available, particularly if abdominal relaxation is induced; if, from overdosage, respiratory paralysis occurs, it will happen within 7 to 10 minutes. For many operations 15 mg (1/4 gr.) of Tubocurarine Chloride are usually sufficient, for abdominal relaxation 20 mg (1/3 gr.) may be required, while 25 mg (2/5 gr.) will paralyse the diaphragm. For children, 0·3 mg (1/200 gr.) per Kg or 2 mg (1/30 gr.) per stone body weight may be used; for aged people, 10 mg (1/6 gr.) is usually adequate.

Tubocurarine may be used for any operation in which muscular relaxation is desirable, e.g. in setting of fractures; but it has proved particularly valuable in abdominal surgery to afford full relaxation without prejudice to the patient's condition. Under its influence, only light anæsthesia is necessary; patients recover and become co-operative quickly; they suffer far less from post-operative shock than if subjected to a deep inhalation anæsthesia; post-operative nausea, vomiting, malaise and respiratory complications are rare; but retention of urine for a few days may occur. In thoracic surgery, it obviates coughing and laryngeal spasm, and the relaxed respiratory muscles render inflation of the lung easier, while, if used with Thiopentone, the inhalation of irritant vapours is avoided.

Tubocurarine is also used to prevent injury or fracture in the convulsive treatment of schizophrenia and in tetanus. A more prolonged action can be gained by giving the drug in Arachis Oil containing 5 per cent. of white Beeswax.

Antidotes.—The most effective antidote to Tubocurarine is Neostigmine, which is twice as powerful as Physostigmine. Neostigmine inhibits the action of cholinesterase and thus permits at the myoneural junction a high concentration of acetylcholine, which can overcome the inhibitory action of Tubocurarine on the muscle receptor, unless a considerable overdose has been given. The effective dose of Neostigmine Methylsulphate for injection is 3 to 5 mg (1/20 to 1/12 gr.) with Atropine 0·6 to 1·2 mg (1/100 to 1/50 gr.) to annul its parasympathetic actions. If the patient is still partially curarized, Neostigmine with Atropine should invariably be given before he leaves the operation room.

Flaxedil.—R.P. 3697. *Tri*-(β-diethylaminoethoxy)-benzene-triethyliodide in 4% neutral solution in water. Ampoules contain 80 mg in 2 Mils.

Flaxedil acts like Tubocurarine by inhibiting Acetylcholine at voluntary neuro-muscular junctions, and 80 mg of Flaxedil has an action almost equal to 15 mg of Tubocurarine; the action lasts 20 to 25 minutes and there is no fall in blood-pressure or side effects. Flaxedil may be mixed with Thiopentone solutions. Neostigmine or Physostigmine is its antidote. **Gallamine** is 1 : 2 : 3-(2′-diethylaminoethoxy)-benzene.

Decamethonium Iodide.—C_{10}. Eulissen. Syncurine. *Bis*-trimethylammonium-decane-diiodide. A white, crystalline salt, easily soluble in water.

Dose.—*By intravenous Injection:*
3 to 5 mg (1/20 to 1/12 gr.). Ampoules contain 5 mg in 2·5 or 5 Mils.

ACTIONS AND USES

Decamethonium Iodide produces in voluntary muscles a neuromuscular block, which passes off in 15 to 25 minutes usually but is sometimes delayed; 3 mg produces the same degree of relaxation as does 15 mg of Tubocurarine. It is used to increase muscular relaxation during light general anæsthesia and can be mixed with Thiopentone solutions. The initial dose is 2 to 3 mg with additions of 1 to 3 mg till the desired relaxation is gained. Means for assisting respiration must be available; Neostigmine is not an antidote, it increases the effect; but Pentamethonium Iodide in 10 times the Decamethonium dose is antidotal. Decamethonium Iodide is also used (0.5 mg per stone body weight) to obviate injury in the convulsive therapy for schizophrenia.

Pentamethonium Iodide.—C_5. Antilusin *Bis*-trimethyl-ammonium-pentane-diiodide.

Dose.—*By intravenous Injection:*
30 to 40 mg (1/2 to 3/5 gr.). Ampoules contain 50 mg. in 5 Mils.

ACTIONS AND USES

Pentamethonium acts by blocking ganglionic cell stations and is an antidote to Decamethonium in 10 times the dose of the latter, but, by blocking the sympathetic ganglia, it lowers blood-pressure rapidly and must be used with care. Its action on ganglia is about 10 times more potent than that of Tetraethyl-ammonium bromide (*see* p. 254) and its effects last much longer (1/2 to 2 hours). It has been used in relieving hypertension and in peripheral ischæmias where it seems to affect the leg more than the arm circulation. It also decreases gastric movements and secretions. Pentamethonium Bromide is also prepared in ampoules containing 40 mg in 2 Mils.

Hexamethonium Bromide.—C_6. *Bis*-trimethyl-ammonium-hexane-dibromide. *Dose.—By intravenous Injection:* 30 to 40 mg (1/2 to 3/5 gr.) or *intramuscularly:* 100 mg (1½ gr.) and **Hexamethonium Iodide** have been used for similar purposes, and, by inhibiting gastric motility and secretion of hydrochloric acid, may be of value in treating peptic ulcer.

Mephenesin.—Myanesin. β-Dihydroxy-γ-(2-methyl-phenoxy)-propane. Issued in 10 Mil ampoules of a 10 per cent. solution. *Dose.*—Intravenously: 5 to 20 Mils. Mephenesin depresses spinal reflexes and acts as a muscle relaxant during light anæsthesia without, in therapeutic doses, impairing respiration or reducing blood pressure; recovery may occur in ten minutes. It is also used orally (0.5 to 1 G), as an elixir, to relieve spasticity in hemiplegia and paralysis agitans.

PERIPHERAL PARASYMPATHETIC STIMULANTS

The drugs which produce the effects of stimulation of the parasympathetic nerves are Physostigmine, Neostigmine, Acetylcholine, Carbachol, Pilocarpine, Muscarine and Arecoline.

Acetylcholine (*not official*).—$HO.(CH_3)_3N.CH_2CH_2.O.CO.CH_3$. The acetyl ester of Choline, used as Acetylcholine Hydrochloride.

Dose.—*Subcutaneously or intramuscularly:* **0·05 to 0·2 G (3/4 to 3 gr.)**

ACTIONS AND USES

Acetylcholine is liberated at the endings of pre-ganglionic autonomic fibres, post-ganglionic *cholinergic* sympathetic fibres, post-ganglionic parasympathetic fibres and voluntary muscle end-plates. Acetylcholine is the chemical transmitter between the nerve ending and the cells it influences, so that a drug which acts as a parasympathetic stimulant potentiates the Acetylcholine either (1) by possessing an action similar to Acetylcholine, e.g. Pilocarpine, Muscarine, Arecoline, Nicotine; or (2) by preventing the hydrolysis of Acetylcholine by cholinesterase into its 1,000 times less active precursor, choline, e.g. Physostigmine, Neostigmine.

Injection of Acetylcholine produces (1) symptoms similar to parasympathetic stimulation, namely, increase in the movements and tone of involuntary muscles, increased secretions from glands and slowing of the heart; (2) a considerable fall in blood-pressure by a direct relaxation of the vascular muscle.

The action of Acetylcholine is too short, owing to its rapid destruction by cholinesterase, to be of more than transient value in treatment, for which Carbachol is more suitable.

Carbacholum.—Carbachol. Carbamylcholine Chloride. Doryl. $H_2N.CO.OCH_2.CH_2.N(CH_3)_3.Cl$.

CHARACTERS.—Colourless, prismatic crystals or powder; hygroscopic and very soluble.

Dose.—*Orally:*

Metric, 1 to 4 mg; Imperial, 1/60 to 1/16 gr.

By subcutaneous injection:

Metric, 0·25 to 0·5 mg; Imperial, 1/240 to 1/120 gr.

Preparation

Injectio Carbacholi.—A sterile solution in Water for Injection containing 0·25 mg (1/240 gr.) in 1 Mil (15 min.).

ACTIONS AND USES

Carbachol has the action of Acetylcholine but is less rapidly hydrolyzed by cholinesterase and thus has a longer effect; also it is active when given orally. It is used in 0·75 per cent. solutions dropped on the conjunctiva to constrict the pupil and to lower intraocular tension in glaucoma. When injected its action lasts 30 or more minutes; it is given to increase the movements and tone of the intestine in meteorism and post-operative intestinal atony, and, by increasing the tone of the bladder, to relieve post-operative urinary retention. By stimulating the vagal endings, it relieves paroxysmal tachycardia.

For its vaso-dilator action, Carbachol has been given orally, or by injection, to relieve hyperpiesia in arterio-sclerosis and chronic nephritis; it has been advised in Raynaud's disease and other arterial spasms, but is only of temporary benefit.

Acetyl-β-methylcholine Chloride.—Methacholine. Mecholin. Mecholyl.

Dose.—*Orally:* **0·05 to 0·5 G (3/4 to 8 gr.)**; *subcutaneously:* **10 to 20 mg (1/6 to 1/3 gr.)** is regarded as more satisfactory than Carbachol as a vagal stimulant in paroxysmal tachycardia; an injection frequently restores a normal rhythm within a few minutes: it is also advised for lowering blood-pressure.

Physostigminæ Salicylas.—Physostigmine Salicylate. Eserine Salicylate. $C_{15}H_{21}O_2N_3,C_6H_4$ (OH).COOH. The Salicylate of an alkaloid, Physostigmine, obtained from Calabar Bean, the seed of Physostigma venenosum. N.O. Leguminosæ.

CHARACTERS.—Colourless or yellow crystals, becoming red on exposure to air and light. *Solubility.*—1 in 100 of water. Aqueous solutions form with dilute NaOH a white precipitate turning pink, or a red solution, and with Fe_2Cl_6 solution, a violet colour.

Dose.—0·6 to 1·2 mg; Imperial 1/100 to 1/50 gr.

Preparations

1. **Injectio Physostigminæ Salicylatis.**—A sterile solution in Water for Injection, containing 0·05% Sodium Metabisulphite. Contains 0·6 mg (1/100 gr.) in 1 Mil (15 min.).
2. **Lamellæ Physostigminæ.**—Discs of Gelatin with Glycerin, each weighing about 1·3 mg (1/50) and containing 0·065 mg (1/1000 gr.) of Physostigmine Salicylate.
3. **Oculentum Physostigminæ.**—Physostigmine Eye Ointment. Physostigmine Salicylate 0·125% in Yellow Soft Paraffin and Wool Fat.

ACTIONS AND USES

Physostigmine Salicylate is absorbed rapidly from mucous membranes. Physostigmine **inhibits the rapid hydrolysis by cholinesterase of Acetylcholine**, the chemical excitor of muscle and gland receptors, into choline; therefore, it increases and prolongs the responses to the liberation of Acetylcholine (1) at the parasympathetic endings in involuntary muscles and secretory glands, including the cholinergic sweat glands, (2) at the pre-ganglionic endings in autonomic ganglia, and (3) at the motor endings in voluntary muscles. Physostigmine can thus reproduce the post-ganglionic parasympathetic stimulation (Muscarine action) and also the pre-ganglionic and voluntary motor stimulation (Nicotine actions) of Acetylcholine. The effects of Physostigmine are the equivalent of stimulation of the parasympathetic or motor nerve endings and will be so described here.

Externally.—Action on the Eye. If the Lamella, the Oculentum, or a drop of 0·1 to 0·4 per cent. Physostigmine Salicylate Solution be applied to the conjunctiva, there may be at first a little painful irritation. In about ten minutes, Physostigmine produces (1) **contraction of the pupil (miotic action)** by stimulating the endings of the oculomotor (3rd) nerve which supply the circular muscle of the iris; the pupil reaches its minimal size in 30 minutes, remains so for about 10 hours and recovers gradually in 3 or 4 days; (2) **decrease of intraocular tension,** because the contracted iris widens the cribriform Spaces of Fontana, and thus filtration from the anterior chamber into the Canal of Schlemm is increased; (3) **accommodation for near objects** by stimulating the ciliary nerve endings and contracting the ciliary muscle which pulls forward the elastic choroid, thus relaxing the tension on the suspensory ligament of the lens and allowing the anterior surface of the lens to become more convex; this effect on accommodation commences in 20 minutes and passes off in from 2 to 4 hours.

Physostigmine is applied on the conjunctiva to diminish intraocular pressure in glaucoma, perforating keratitis, etc.; to treat paralysis of the iris and ciliary muscle, e.g. after diphtheria; to prevent adhesions of the iris in corneal ulcer; to accelerate recovery from the effects of Atropine; or to diminish the entrance of light in photophobia, etc. It is used alternately with Atropine to break down adhesions of the iris.

Internally.—Action on involuntary muscles.—When given by mouth or injected subcutaneously Physostigmine *increases the movements and tone of the involuntary muscles* controlled by parasympathetic nerves. By its action at the vagal endings, it augments the tone and peristalsis of the stomach and intestines and thus produces purgation, which is often accompanied by colic owing to tonic contraction of portions of the bowel.

For this stimulant action, Physostigmine Salicylate is used commonly as a hypodermic injection in the treatment of meteorism, intestinal atony, or paralytic ileus following abdominal operations.

Physostigmine also increases the tone of the bronchioles, uterus and bladder, and has been used in paralysis of the vesical sphincters.

The **heart is slowed** by stimulation of the vagal endings, but the blood-pressure may not be affected possibly owing to constriction of the splanchnic vessels through activation of the Acetylcholine in the sympathetic ganglia.

Action on Glands.—Physostigmine **increases the secretions of glands** under parasympathetic control, namely the salivary, lachrymal, bronchial and intestinal glands, but its action is less than that of Pilocarpine. The secretion of the sweat glands (sympathetic but cholinergic innervation) is also augmented.

Action on Voluntary Muscles.—Physostigmine by inactivating cholinesterase increases the excitor effect of Acetylcholine on the receptors of voluntary muscles; it may produce fibrillary twitchings and these are often seen in the lower eyelid when Physostigmine is applied on the conjunctiva. Because of this action, it lowers the excitor threshold of efferent motor stimuli and Physostigmine, in hypodermic doses of 1/60 to 1/50 gr. which act for 4 to 5 hours, has proved useful in hemiplegia, myasthenia gravis and in other forms of paralysis in which it improves the muscular responses and decreases wasting; but its actions on the parasympathetic system are a disadvantage; these may be counteracted by 1/100 gr. of Atropine Sulphate. Physostigmine may also be used as an antidote to Tubocurarine (*see* p. 321) but Neostigmine is twice as powerful and therefore preferable.

Action on Cerebrum, Medulla and Cord.—Physostigmine in toxic doses produces a brief stimulation of the cortex, medullary centres and spinal cord, followed by depression. The **respiratory centre** is at first stimulated, but contraction of the bronchioles causes dyspnœa and subsequent depression of the centre is the cause of death.

Neostigminæ Bromidum.—Neostigmine Bromide. Prostigmin. The dimethylcarbamic ester of 3-hydroxyphenyltrimethyl-ammonium bromide. $C_{12}H_{19}O_2N_2Br$.

CHARACTERS.—A white, crystalline, soluble powder; taste bitter.
Dose.—*Orally:* **Metric, 10 to 20 mg; Imperial, 1/6 to 1/3 gr.**

Neostigminæ Methylsulphas.—Neostigmine Methylsulphate. Prostigmin.

CHARACTERS.—A white, crystalline powder; taste bitter. Soluble 1 in 10 of water.

Dose.—*By subcutaneous or intramuscular injection:*
Metric, 0·5 to 2 mg; Imperial, 1/120 to 1/30 gr.

Preparation

Injectio Neostigminæ Methylsulphatis.—A sterile solution in Water for Injection for subcutaneous or intramuscular use, containing 0·5 mg (1/120 gr.) in 1 Mil (15 min.).

ACTIONS AND USES

Neostigmine acts like Physostigmine by inhibiting hydrolysis of Acetylcholine by cholinesterase; its effects are less powerful on the parasympathetic, but greater on the voluntary motor receptors, and more prolonged than those of Physostigmine.

For its parasympathetic stimulant action, the Injection is given hypodermically or intramuscularly to augment the movements and tone of the intestine in flatulent distension and paralytic ileus, of the ureters to expel calculi, and of the bladder in retention of urine. Drops of a 5 per cent. solution of Neostigmine Methylsulphate are effective in lowering intraocular tension in glaucoma.

The stimulant action on voluntary muscle is utilized in the treatment of **myasthenia gravis**, in which disease insufficient Acetylcholine is formed by a nerve stimulus to escape destruction and excite the muscle, although it is sensitive. A hypodermic injection of Neostigmine Methylsulphate will restore a normal muscle curve within fifteen minutes, and Neostigmine Bromide, orally, may maintain this effect for about eight hours; swallowing of food is also facilitated. A maintenance dosage of Neostigmine Bromide should be arranged and its undesirable parasympathetic effects annulled by Atropine 0·4 to 0·6 mg (1/150 to 1/100 gr.), given before, or with, the Neostigmine.

Neostigmine Methylsulphate is also valuable as an antidote to Tubocurarine; by inhibiting cholinesterase, it facilitates the penetration through the Tubocurarine block of sufficient Acetylcholine to influence the muscle. It is advisably given by injection in dose of 2 or 4 mg (1/30 or 1/15 gr.) with Atropine Sulphate 0·6 mg (1/100 gr.) at the conclusion of operations when Tubocurarine has been used.

Ethyl Pyrophosphate.—Tetraethyl Pyrophosphate (T.E.P.P.). A colourless oil given in 2 or 5% solution in propylene glycol.

Dose.—*Orally:*

8 to 12 mg (1/8 to 1/5 gr.) daily, divided into 2 or 3 doses.

Intramuscularly:

1·25 mg (1/50 gr.) in 0·5% solution in propylene glycol.

ACTIONS AND USES

This compound is an antagonist of cholinesterase, and 10 to 18 mg daily by mouth is equivalent in effect to 100 to 150 mg of

Neostigmine orally and lasts longer (about 24 hours). It has been used in myasthenia gravis. It has side effects like those of Neostigmine.

Di-Isopropyl-Fluorophosphonate (D.F.P.).

Dose.—*Intramuscularly:*

1 to 2 Mils of 0·1% solution in sterile Arachis Oil.

ACTIONS AND USES

Alkyl fluorophosphonates inhibit the action of cholinesterase. This compound acts slowly and is liable to cumulation. Intramuscular injections of 2 mg cause increased rhythmic movements of the small and large intestines within an hour and they last from 3 to 5 hours; it is used for post-operative paralytic ileus. In myasthenia gravis, its action is delayed for several days, but it improves the muscular power, dysphagia and chewing; from 0·5 to 2 Mils are given daily. One drop of a 0·1 per cent. solution not more than thrice daily is used as a miotic for glaucoma.

Pilocarpinæ Nitras.—Pilocarpine Nitrate. $C_{11}H_{16}N_2O_2,HNO_3$. The nitrate of an alkaloid, Pilocarpine, obtained from the leaves of Pilocarpus microphyllus (Jaborandi), and other species. N.O. Rutaceæ.

CHARACTERS.—A white, crystalline powder. *Solubility.*—1 in 8 of water. With H_2SO_4 yields a colourless solution turning green on adding K_2CrO_4; an aqueous solution with dilute H_2SO_4,H_2O_2, benzene and K_2CrO_4 solution gives, when shaken, bluish-violet in the benzene.

Dose.—Metric, 3 to 12 mg; Imperial, 1/20 to 1/5 gr.

ACTIONS AND USES

Pilocarpine produces the stimulant effects of Acetylcholine on post-ganglionic parasympathetic and cholinergic sympathetic nerve endings but does not have its stimulant action on voluntary motor receptors or upon pre-ganglionic autonomic synapses.

Externally.—Pilocarpine Nitrate, applied in solution (1 to 2 per cent.) to the conjunctiva, causes (1) **contraction of the pupil** by stimulating the third nerve receptors; (2) **reduction of intraocular tension** in consequence; and (3) **accommodation of the eye for near vision** by stimulating the ciliary nerves. Because it is less irritant to the conjunctiva, it is sometimes used instead of Physostigmine.

Pilocarpine is alleged to increase the growth of hair, but has no apparent effect in alopecia areata.

Internally.—Action on Glands. The action of Pilocarpine is predominantly upon the secretory glands. Within 10 to 15 minutes if given by mouth, or 5 minutes if injected hypodermically, Pilocarpine produces a great increase of the secretions which are under cholinergic nervous control. **Increased salivary secretion** occurs first owing to stimulation of the chorda tympani and glosso-pharyngeal endings in the glands; hence it is of some service in xerostomia or dryness of the mouth. **Profuse perspiration** follows from stimulation of the sudoriparous nerves which, although derived from the sympathetic, react to cholinergic drugs. The **rapid and powerful diaphoretic** action progresses from the head and neck downwards, is accompanied by flushing of the skin, and the excessive sweat commonly soaks the bedclothes; the action persists from 2 to 5 hours, and, as the result of the increased loss of heat, the temperature falls. The sweat, amounting often to from 2 to 3 litres, consists mainly of water, but this carries with it proportionally larger amounts of nitrogenous excretions, chiefly urea.

Pilocarpine was formerly used to rest the kidneys and to provide for excretion during nephritis, uræmia and suppression of urine. It was also used to drain fluid from the body in œdema. For both these purposes, its use has been abandoned.

Pilocarpine also increases the mucous secretions of the nose, throat and bronchioles, the tears, and the gastric, pancreatic and intestinal secretions. These effects are of small practical utility; in bronchitis, small doses by mouth may give relief by liquefying the bronchial secretions, but there is a risk of causing pulmonary œdema. Pilocarpine has no direct influence on the secretion of bile, milk or urine.

Action on Involuntary Muscles.—Pilocarpine increases the tone and movements of the stomach and intestines, thus causing nausea, colic and purgation; constricts the bronchioles; and augments the tone of the ureters, bladder, spleen and uterus.

The rate of the heart in animals is slowed by stimulation of the vagal endings and the blood-pressure falls; but, in man, this inhibitory phase may be brief or entirely absent and is replaced by cardiac acceleration and a rise in blood-pressure; the cause may be increased secretion of Adrenaline.

Pilocarpine is not suitable to treat intestinal atony because of the undesirable sweating.

The action on the central nervous system is depressant but is seen only after toxic doses.

Meprochol (B.P.C.).—Trimethyl-methoxy-propenyl-ammonium bromide. *Dose.—By subcutaneous or intramuscular injection:* 3 mg (1/20 gr.).

Meprochol is a stimulant of cholinergic receptors and has been used in post-operative intestinal atony.

Muscarine (*not official*).—An alkaloid obtained from a toadstool, Amanita muscaria (Fly Agaric). Muscarine has, like Pilocarpine, the actions of Acetylcholine in stimulating post-ganglionic parasympathetic and cholinergic sympathetic endings or receptors; it does not possess the nicotine-like actions of Acetylcholine on pre-ganglionic autonomic endings or on voluntary motor end plates.

Arecoline, from Areca Catechu, also acts like Pilocarpine, but has about three times its potency.

PERIPHERAL PARASYMPATHETIC DEPRESSANTS

The alkaloids which inhibit the actions of Acetylcholine are Atropine, Hyoscyamine and Hyoscine, obtained from Belladonna, Stramonium, Datura, and Hyoscyamus. The characteristic action of these alkaloids is equivalent to paralysis of the parasympathetic and cholinergic sympathetic endings. They act even after the nerves have been cut and allowed to degenerate, therefore the effect must be to render the cells insensitive to Acetylcholine.

Belladonnæ Herba.—Belladonna Herb. Belladonna Leaf. The dried leaves and other aerial parts of Atropa Belladonna and/or Atropa acuminata. N.O. Solanaceæ.

CHARACTERS.—Pale yellowish-green, large, ovate leaves and drooping flowers on stems. Contains not less than 0·3% of alkaloids.
COMPOSITION.—The alkaloids *hyoscyamine; atropine; hyoscine, belladonnine.*

Belladonna Præparata.—Prepared Belladonna Herb. Powdered Belladonna Herb in fine powder adjusted to contain 0·3% of alkaloids, calculated as hyoscyamine. Contains in 200 mg (3 gr.), 0·6 mg (1/100 gr.) alkaloids.

Dose.—Metric, 30 to 200 mg; Imperial, 1/2 to 3 gr.

Preparations

1. **Extractum Belladonnæ Siccum.**—Alcoholic (70%). *Standardized* to contain 1% of the alkaloids. Contains in 60 Mg (1 gr.) 0·6 mg (1/100 gr.) alkaloids.

Dose.—Metric, 15 to 60 mg; Imperial, 1/4 to 1 gr.

2. **Tinctura Belladonnæ.**—Belladonna Herb, 10%, in Alcohol 70%; by percolation. *Standardized* to contain 0·03% alkaloids. Contains in 1 Mil (15 min.) 0·3 mg (1/200 gr.) alkaloids.

Dose.—Metric, 0·3 to 1 Mils; Imperial, 5 to 15 min.

Belladonnæ Radix.—Belladonna Root. The dried root of Atropa Belladonna and/or Atropa acuminata. Contains not less than 0·4% of alkaloids.

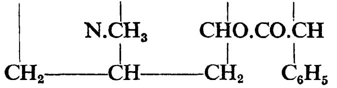
CHARACTERS.—Nearly cylindrical, wrinkled, greyish-brown pieces, entire or longitudinally split; internally whitish, starchy. Taste slightly bitter.

COMPOSITION.—The alkaloids, *hyoscyamine*, *atropine*, *scopolamine* or *hyoscine*, *belladonnine*.

Preparations

1. **Extractum Belladonnæ Liquidum.**—Aqueous and alcoholic (80%). *Standardized* to contain 0·75% alkaloids.
2. **Linimentum Belladonnæ.**—An extract of an alcoholic percolate, with 5% Camphor. Contains 0·375% of alkaloids.
3. **Suppositoria Belladonnæ.**—Each contains 0·15 Mil (2½ min.) of Liquid Extract in Oil of Theobroma. 1 mg (1/60 gr.) of alkaloids in each.

Atropina.—Atropina. $C_{17}H_{23}NO_3$. An alkaloid, *dl*-hyoscyamine, from Atropa Belladonna, Hyoscyamus muticus or other solanaceous plants.



CHARACTERS.—Colourless, acicular crystals. *Solubility.*—1 in 500 of water; readily in alcohol 90%, in chloroform and in ether. Aqueous solution alkaline, and yields with auric chloride a citron-yellow precipitate (M.P. 133–139° C); distinction from hyoscyamine (M.P. 165° C). Atropine evaporated with HNO_3 to dryness on water-bath gives yellowish residue, which becomes violet with alcoholic KOH solution. It can be chemically resolved into *tropine*, $C_8H_{15}NO$, and *tropic acid*, $C_9H_{10}O_3$.

Atropinæ Sulphas.—Atropine Sulphate. $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$. The Sulphate of the alkaloid Atropine.

CHARACTERS.—Colourless crystals, somewhat hygroscopic. *Solubility.*—1 in 1 of water; 1 in 4 of alcohol 90%.

Dose.—Metric, 0·25 to 1 mg; Imperial, 1/240 to 1/60 gr.

Preparations

1. **Injectio Atropinæ Sulphatis.**—A sterile solution in Water for Injection for subcutaneous injection. Contains 0·6 mg (1/100 gr.) in 1 Mil (15 min.).
2. **Injecto Morphinæ et Atropinæ.**—Contains 0·6 mg (1/100 gr.) Atropine Sulphate and 10 mg (1/6 gr.) Morphine Sulphate in 1 Mil (15 min.) of Water for Injection.

Dose.—*By subcutaneous injection:*

Metric, 0·5 to 1 Mil; Imperial, 8 to 15 min.

3. **Tabellæ Atropinæ Sulphatis.**—0·6 mg (1/100 gr.) in each.
4. **Lamellæ Atropinæ.**—Discs of Gelatin with Glycerin, each weighing about 1·3 mg (1/50 gr.), and containing 0·013 mg (1/5000 gr.) of Atropine Sulphate.

5. **Oculentum Atropinæ.**—Atropine Eye Ointment. Atropine Sulphate 0·25% with Yellow Soft Paraffin and Wool Fat.
6. **Oculentum Atropinæ cum Hydrargyri Oxido.**—Atropine Sulphate 0·125% with Yellow Mercuric Oxide 1% with Yellow Soft Paraffin and Wool Fat.

ACTIONS AND USES

Atropine, which is optically inactive, consists of *d*-**Hyoscyamine,** which acts mainly on the central nervous system, and *l*-**Hyoscyamine,** which acts centrally and also on parasympathetic endings. The chief central actions of Atropine are initial stimulation of the cerebral motor area and of the respiratory centre, followed by depression. The peripheral action will be referred to as paralysis of the post-ganglionic parasympathetic and cholinergic sympathetic nerve endings, but the fundamental action of Atropine is to **antagonize** and prevent the stimulant property of **Acetylcholine,** the chemical transmitter formed by efferent nervous impulses at these places. Atropine does not inhibit the action of Acetylcholine on autonomic ganglia or on voluntary muscle.

Externally.—Atropine can be absorbed by the skin from alcoholic or oily solutions, such as Liniments or Ointments, and has been credited with having a local analgesic action in muscular rheumatism. Atropine Sulphate is rapidly absorbed by mucous membranes or raw surfaces, but it has no local anæsthetic action on the conjunctiva or when injected, and it is doubtful if the Suppository has any anodyne action on hæmorrhoids.

Actions on the Eye.—If the Lamella or a drop of 1 per cent. Atropine Sulphate is placed on the conjunctiva, it produces (1) **full dilatation of the pupil (mydriatic action)** and loss of the light reflex, because Atropine paralyses the third nerve endings which supply the circular muscle of the iris. This action commences in 10 minutes, reaches a maximum in 1/2 to 1 hour, but persists, so that the normal size of the pupil may not return until after 5 or 7 days; (2) **increased intraocular tension,** because the dilated iris constricts the Spaces of Fontana, and this retards filtration of fluid from the anterior chamber to the Canal of Schlemm: Atropine may thus cause glaucoma; (3) **accommodation for infinity** (cycloplegia); Atropine paralyses the ciliary endings, therefore the ciliary muscle relaxes and enables the elastic choroid to increase the tension on the suspensory ligament so that the anterior surface of the lens becomes flatter and the eye is focused for infinity: the action on accommodation occurs more slowly, it reaches a maximum in 2 to 4 hours and passes off in from 3 to 4 days; (4) **decreased lachrymal secretion** by paralysing the secretory endings.

Atropine is applied on the conjunctiva to facilitate ophthalmoscopic examination of the retina and to paralyse accommodation in order to estimate the refraction of the lens. For adults its effects are too prolonged, but Atropine is valuable to ensure complete paralysis of accommodation in young children. It is also used to dilate and rest the iris in iritis and to prevent or break down adhesions which may occur from corneal ulcer.

Internally.—Action on Glands. Atropine in dose of 1/100 gr. by mouth, or hypodermically, paralyses parasympathetic (cholinergic) secretory endings. It **reduces the salivary and mucous secretions** of the mouth and throat, and causes a sensation of thirst. For this reason Atropine is of value in treating the excessive salivation which arises during pregnancy or from cerebral disease or mercurial poisoning. Sprays containing 1/3 gr. Atropine in 1 fl. oz. check excessive secretion of nasal mucus.

Atropine **diminishes the gastric secretions** by paralysing the secretory vagal endings, the hydrochloric-acid secretion is particularly reduced and, as a result, the pancreatic secretion is weak in enzymes, but it is also reduced in quantity by paralysis of the vagal endings in the gland. Atropine also diminishes the intestinal secretions, but it does not influence the biliary secretion.

For its action in reducing the acidity and the amount of gastric secretion, Atropine Sulphate or the Tincture of Belladonna is prescribed in the treatment of **hyperchlorhydria** and of **gastric and duodenal ulcer**, especially in the evening to prevent secretion during the night.

The **bronchial mucous secretion is reduced**, hence Atropine is given to prevent bronchial secretion due to inhalation of the irritant vapour of Ether, and full doses are recommended in treating pulmonary œdema.

The **sweat secretion is inhibited** by a paralysis of the sympathetic (cholinergic) endings. Atropine is therefore **anhydrotic**. Local sweating may be treated by an ointment (2 per cent.) of Atropine.

The **milk secretion** is not influenced by Atropine.

Action on Involuntary Muscles.—Atropine, by paralysing the vagal endings, **reduces the tone of involuntary muscles.** In the stomach and intestines, Atropine does not alter the normal peristalsis, but, by lowering the tone of the muscle, it **abolishes spasmodic contractions** which cause colic and griping. Atropine or the Dry Extract of Belladonna is, therefore, commonly prescribed in pills to prevent or alleviate the griping associated with the action of purgatives and to allay colic; they are useful also in types of constipation associated with increased intestinal tone, and to relieve infantile spasm of the pylorus, spastic ileus and colon; further, an injection of Atropine Sulphate frequently facilitates reduction of a hernia by relaxing intestinal spasm. Atropine may sometimes relieve the gastric crises of tabes.

Atropine in a similar manner relaxes spasm of the involuntary muscles of the spleen, bile duct, ureters, bladder and uterus. Given by injection,usually along with Morphine, Atropine affords great relief from the spasmodic pain of **biliary and renal colic** during the passage of a calculus. It is also valuable to reduce spasmodic contractions of the genito-urinary passages in various conditions such as chordee, nocturnal incontinence of children, and vesical spasm resulting from uric-acid diathesis, cystitis and prostatitis. Fissure of the anus and spasm of the anal sphincter may be relieved by the Belladonna Suppository.

The **bronchioles are widely dilated** owing to paralysis of the vagal innervation by Atropine, which is sometimes used to relieve spasmodic asthma and emphysema either by hypodermic injection, by inhalation in the form of a spray (0·05 per cent.), or by mouth. Adrenaline or Ephedrine, to stimulate the sympathetic nerve endings, is usually prescribed as well.

Action on the Heart and Circulation.—At first by stimulating the medullary vagal centre, Atropine may retard the cardiac rhythm slightly, but this phase is transient. Soon the auricles and **ventricles beat more rapidly** because the vagal endings are paralysed, and therefore, the rate may be accelerated very much. In consequence, the **blood-pressure rises** to a moderate extent. Toxic doses of Atropine are direct depressants to cardiac muscle and, in poisoning, the heart becomes slow and weak but survives the respiratory failure. Atropine dilates superficial blood-vessels, especially those of the face and neck, and may cause an *erythematous rash*, followed by desquamation; the action is ascribed to stimulation of some, probably central, vaso-dilator mechanism.

Atropine has a restricted therapeutic value in heart disease. When bradycardia or slow rhythm is due to excessive vagus action or to nervous heart-block or is post-diphtheritic in origin, Atropine frequently proves useful in accelerating the rate, but, as may occur in Adams-Stokes' disease, it may increase the auricular but not the ventricular rate. Vaso-vagal syncope, sinus irregularity or sino-auricular heart-block is commonly arrested by small doses of Atropine or Belladonna. If excessive dosage of Digitalis has been given, Atropine will abolish the effects of excessive vagal stimulation by Digitalis.

A hypodermic injection of Atropine (1/100 gr.) is usually given, in association with Morphine (1/4 gr.), half an hour **before the induction of general anæsthesia.** The object of the Atropine is to prevent reflex inhibition of the heart through the vagus and to diminish salivary and bronchial secretion and to counteract depression of the respiratory centre; while the Morphine serves to depress the sensory area of the cortex, to allay apprehension and induce somnolence.

Action on the Cerebrum, Medulla and Cord.—In full doses (1/100 to 1/60 gr.), Atropine is a **stimulant of the cerebral motor area**; the psychical faculties, intellect and sensory areas are uninfluenced. The motor cortex is more easily stimulated and the cerebral reflexes are more active. Patients may show restlessness, talkativeness with hallucinations, and purposeless muscular movements which may be inco-ordinate. Larger doses may induce active delirium or maniacal excitement, but this stimulant stage passes into one of **depression**, and a condition of stupor and coma follows.

On account of its cerebral action, Atropine was classed as a **deliriant narcotic**, but the stage of motor excitement renders it unsuitable therapeutically.

The **medullary centres are stimulated** by therapeutic doses. The **respiratory centre** is most influenced and breathing becomes more frequent and usually deeper. With doses above 1/50 gr. stimulation is often succeeded by depression, and the breathing is rendered slow, shallow and irregular. Toxic doses cause death by paralysis of the centre.

Its stimulant action on the respiratory centre renders Atropine valuable to prevent respiratory failure during anæsthesia, but, for treatment, more active respiratory stimulants are now available.

Stimulation of the vagus centre accounts for the initial but transient slowing of the heart. Stimulation of the vaso-motor centre contributes to the rise of blood-pressure produced by acceleration of the heart; toxic doses subsequently depress the centre, and blood-pressure is low in poisoning from Atropine. Toxic doses may also produce a rise in temperature; this is due to stimulation of the thermogenetic centre assisted by the reduction of sweating.

The spinal cord is influenced only by toxic doses, which first increase and finally depress the reflexes.

Young children are less sensitive to the action of Atropine than adults, and may require slightly larger doses than those proportional to their weights. In aged persons, also, the response to Atropine is less.

Excretion of Atropine.—Atropine is excreted unchanged in the urine, at first rapidly and then more slowly, for about 2 days. During its excretion Atropine serves to relieve spasmodic contractions in the ureter and bladder. Small quantities pass through the placenta to the fœtus.

Atropinæ Methonitras (B.P.C.).—Atropine Methonitrate. Eumydrin. *Dose.*—1 to 2 mg (1/60 to 1/30 gr.). This is less toxic than Atropine and more successful for the treatment of infantile vomiting from hypertrophic pyloric stenosis as a 1 in 10,000 solution; this is given ½ hour before each feed, starting with 2 Mils (30 min.) and increasing to 5 Mils (75 min.). It is also available as Lamellæ. The dehydration and alkalosis must also be treated.

Lachesinæ Chloridum (B.P.C.).—Lachesine. β-benzilyloxyethyldimethylethylammonium chloride. Lachesine, a white soluble powder, is used in 1% solutions as drops to dilate the pupil and accommodate the lens for infinity. It is not irritant to the conjunctiva, as Atropine sometimes is; its mydriatic and cycloplegic actions are maximal in 1/2 to 1 hour and begins to pass off after 6 hours, although some effect may last for 2 days.

Homatropinæ Hydrobromidum.—Homatropine Hydrobromide. $C_{16}H_{21}NO_3,HBr$. The hydrobromide of an alkaloid prepared from tropine and mandelic acid.

CHARACTERS.—A white crystalline powder. *Solubility.*—1 in 6 of water. Treated with HNO_3 and alcoholic KOH, a reddish-yellow colour is produced, not changing to violet (distinction from Atropine). Homatropine gives yellow then brick-red if warmed with alcoholic (60%) $HgCl_2$ solution.

Preparation

Lamellæ Homatropinæ.—Discs of Gelatin, with some Glycerin, each weighing about 2·1 mg (1/32 gr.) and containing 0·65 mg (1/100 gr.) Homatropine Hydrobromide.

ACTIONS AND USES

The actions of Homatropine are **similar to those of Atropine,** but weaker. It is used in ophthalmic practice as a **mydriatic,** either as a 1 or 2 per cent. solution or as the Lamellæ, its advantages being that whilst it dilates the pupil more quickly (in a 1/4 to

1/2 an hour) than Atropine, its effects pass off in 12 to 24 hours; accommodation is paralysed after an hour and has recovered in about 12 hours. Homatropine has, therefore, much less tendency to increase intraocular tension. It is used for examination of the retina and lens and to rest the pupil in iritis when there is a risk of glaucoma.

Hyoscyamus.—Hyoscyamus Leaves. Henbane Leaves. The dried leaves and flowering tops of Hyoscyamus niger. N.O. Solanaceæ.

CHARACTERS.—Pale-green, ovate, hairy leaves with acute apex and toothed margin; odour characteristic; taste bitter, acrid.

COMPOSITION.—The active alkaloids are (1) *l-hyoscyamine*, $C_{17}H_{23}NO_3$; (2) *hyoscine* or *scopolamine*, $C_{17}H_{21}NO_4$, and (3) *atropine*. Contains not less than 0·05% of alkaloids as hyoscyamine.

Preparations

1. **Extractum Hyoscyami Siccum.**—Dry Extract of Hyoscyamus, alcoholic (70%). *Standardized* to contain 0·3% of alkaloids. 60 mg (1 gr.) contains 0·18 mg (1/350 gr.) alkaloids.
Dose.—Metric, 16 to 60 mg; Imperial, 1/4 to 1 gr.
2. **Pilula Colocynthidis et Hyoscyami.**—Contains about 12·5% Extract of Hyoscyamus. *See* p. 174.
Dose.—Metric, 0·25 to 0·5 G; Imperial, 4 to 8 gr.
3. **Extractum Hyoscyami Liquidum.**—Liquid Extract. Prepared by percolation with 70% Alcohol. Contains 0·05% of alkaloids. 0·4 Mil (6 min.) contains 2 mg (1/320 gr.) alkaloids.
Dose.—Metric, 0·2 to 0·4 Mil; Imperial, 3 to 6 min.
4. **Tinctura Hyoscyami.**—Liquid Extract 10% in Alcohol 70%. Contains 0·005% of alkaloids. 4 Mils (60 min.) contains 2 mg (1/320 gr.) alkaloids.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

Hyoscinæ Hydrobromidum.—Hyoscine or Scopolamine Hydrobromide. $C_{17}H_{21}NO_4,HBr,3H_2O$. Obtained from Hyoscyamus Leaves, and other solanaceous plants.

CHARACTERS.—Colourless, rhombic crystals. *Solubility.*—1 in 4 of water. Alkaloid dissolved in dilute HCl gives with auric chloride solution a yellow crystalline precipitate (M.P. 198–200° C.). With HNO_3 and alcoholic KOH it gives violet colour like Atropine.
Dose.—Metric, 0·3 to 0·6 mg; Imperial, 1/200 to 1/100 gr.

Preparations

1. **Injectio Hyoscinæ Hydrobromidi.**—A sterile solution for subcutaneous injection in Water for Injection. Contains 0·4 mg (1/160 gr.) in 1 Mil (15 min.).
2. **Oculentum Hyoscinæ.**—Hyoscine Eye Ointment. Contains 0·125% in Yellow Soft Paraffin and Wool Fat.

ACTIONS AND USES

The actions and uses of Hyoscyamus **resemble those of Belladonna and Atropine**. The special distinctions are as follows:

(1) Hyoscyamus, as it contains more Hyoscine, is more depressant to the motor area than Belladonna. (2) Its tone-relaxing or antispasmodic action on the bowel is better, and Dry Extract of Hyoscyamus is often prescribed with drastic purgatives in pills. (3) Its peripheral action on cholinergic autonomic nerve endings is slightly greater; the Tincture relieves irritability of the bladder, and to check pain in cystitis, renal or biliary calculus.

Hyoscine differs from Atropine in producing **depression of the cerebral motor area** and spinal reflexes without preliminary stimulation, and is used chiefly as a motor sedative. It also **impairs memory** for recent events. In dose of 1/100 gr. orally, it is an effective **preventive of sea-sickness.** When injected it soon causes muscular lethargy, decreases excitement and produces drowsiness or sleep which lasts 6 to 8 hours, but it does not relieve pain. Excessive doses depress the respiratory centre, without initial stimulation.

Hyoscine is injected hypodermically as a motor sedative in maniacal excitement, delirium, delirium tremens, and in treating the Alcohol or Morphine habit. In chorea and paralysis agitans Hyoscine is valuable in reducing movements and tremors, while in post-encephalitic Parkinsonism it is used to relieve the rigidity and muscular hypertonus, to reduce salivation and to treat ocular crises; it is not equally successful in relieving the tremors. In post-encephalitic cases, it should be given after meals to avoid disturbance of eating owing to the dryness of the mouth, and the dose increased until the maximum benefit, short of causing uncomfortable tachycardia, is attained.

Hyoscine 0·45 mg (1/150 gr.) with Morphine 16 mg (1/4 gr.) is used as a motor sedative and basal narcotic prior to operations and is sometimes given at the end of the first stage of labour in obstetric practice (**twilight sleep**). The Morphine allays anxiety and pain, while the Hyoscine reduces movement and reflexes; but both alkaloids are respiratory depressants. When used in parturition, these alkaloids pass into the fœtal circulation, and respiration is often difficult to arouse at birth. Hyoscine, like Atropine, paralyses parasympathetic nerve endings, but its action is more rapid, powerful and brief. In 0·2 per cent. solution, or as the Oculentum, it is employed as a **mydriatic**, as its action is a little quicker—1/2 hour—and less prolonged—3 to 5 days—than that of Atropine; accommodation is paralysed in 1 hour and recovers in 3 days.

Stramonium.—Stramonium Leaves. The dried leaves and flowering tops of Datura Stramonium and D. Tatula, N.O. Solanaceæ.

CHARACTERS—Greyish-green, ovate leaves, with petioles, an acute apex and unequal base; margin sinuate, dentate. Odour characteristic; taste unpleasant, bitter.

COMPOSITION.—Chiefly *hyoscyamine* along with *atropine* and *hyoscine* (scopolamine). Contains not less than 0·25% of alkaloids calculated as hyoscyamine.

Preparations

1. **Extractum Stramonii Siccum.**—Made by drying an alcoholic (95%) percolate and adding starch to yield a Dry Extract containing 1% alkaloids. 60 mg (1 gr.) contains 0·6 mg (1/100 gr.) alkaloids.
Doses.—Metric, 15 to 60 mg; Imperial, 1/4 to 1 gr.
In post-encephalitic and similar conditions:
Metric, 60 to 500 mg; Imperial, 1 to 8 gr.

2. **Extractum Stramonii Liquidum.**—Made by percolation with Alcohol 45%. Contains 0·25% alkaloids. 0·2 Mil (3 min.) contains 0·5 mg (1/120 gr.) alkaloids.
Dose.—Metric, 0·03 to 0·2 Mil; Imperial, 1/2 to 3 min.

3. **Tinctura Stramonii.**—Liquid Extract 10% in Alcohol 45%. Contains 0·025% alkaloids. 2 Mils (30 min.) contain 0·5 mg (1/120 gr.) alkaloids.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.

ACTIONS AND USES

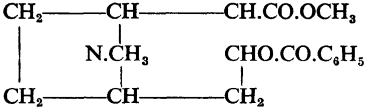
Stramonium acts like **Atropine**, but more efficiently paralyses the vagus terminations in the bronchi and thus relaxes their muscles. Stramonium is used for the treatment of spasmodic affections of the bronchi, such as whooping-cough and asthma. The Tincture in mixture form may be given to prevent or lessen the spasmodic attacks; formerly the smoke of the smouldering leaves in cigarettes or powders was inhaled during the paroxysm. The Dry Extract, given thrice daily by mouth in post-encephalitic Parkinsonism, relieves the muscular rigidity, diminishes tremor, and improves the speech and mentality; it is preferable to frequent hypodermic injections of Hyoscine and, if dryness of the mouth becomes objectionable, Pilocarpine Nitrate 1/10 gr. may be prescribed. The Dry Extract is used also for paralysis agitans.

Datura Folia and *Semina* are used in India and the Eastern colonies as substitutes for Stramonium and Belladonna.

LOCAL ANÆSTHETICS

Drugs which prevent the conduction of sensory impulses by nerves, and thus produce anæsthesia in the area supplied by the nerves upon which they act.

Cocaina.—Cocaine. Methyl-benzoyl-ecgonine. $C_{17}H_{21}NO_4$. An alkaloid from the leaves of Erythroxylum Coca and its varieties. N.O. Erythroxylaceæ; or synthesized from ecgonine.



CHARACTERS.—Colourless, monoclinic prisms; no odour; taste bitter, followed by numbness. *Solubility.*—Almost insoluble in water; 1 in 24 of olive oil; 1 in 120 of liquid paraffin.

Cocainæ Hydrochloridum.—Cocaine Hydrochloride. $C_{17}H_{21}NO_4,HCl$.

CHARACTERS.—Colourless, prismatic crystals; no odour; taste bitter, followed by numbness. *Solubility.*—2 in 1 of water; insoluble in olive oil. A 1% solution gives with drops of 3% chromium trioxide a yellow precipitate. Solution with N/10 $KMnO_4$ and dilute H_2SO_4 gives violet colour.

Dose.—Metric, 8 to 16 mg; Imperial, 1/8 to 1/4 gr.

Preparations

1. **Lamellæ Cocainæ.**—Discs of Gelatin with Glycerin, each weighing about 3·5 mg (1/20 gr.) and containing 1/3 mg (1/50 gr.) of Cocaine Hydrochloride.
2. **Oculentum Cocainæ.**—Cocaine Eye Ointment, contains 0·25% in Yellow Soft Paraffin and Wool Fat.
3. **Trochiscus Krameriæ et Cocainæ,** 3 mg (1/20 gr.) in each.
4. **Suppositoria Cocainæ,** 15 mg (1/4 gr.) in each.

ACTIONS AND USES

Cocaine is toxic to tissue cells. Strong solutions (over 5 per cent.) if injected may cause a local necrosis, and even a 1 per cent. solution on the conjunctiva causes a slight necrosis of the epithelial cells which collect as "matter" at the inner canthus. Cocaine and other local anæsthetics produce a selective sensory paralysis. The blocking of the sensory impression follows most rapidly in smallest nerve fibres having a thin myelin sheath. No detectable change occurs in the nerve fibres and the anæsthesia is temporary.

Cocaine is a **valuable surface anæsthetic**, but it is rarely injected because of its local and general toxic effects. For injection, Procaine and other substitutes have replaced Cocaine. The alkaloid Cocaine in ointments (4 per cent.) is absorbed slowly by the skin; Cocaine Hydrochloride is readily absorbed from mucous membranes or raw surfaces. If Cocaine Hydrochloride solution (1 to 2 per cent.) be applied to a mucous membrane, there follows **within 5 minutes abolition of the sense of pain** and diminution of the sense of touch in this area; the temperature sense is less affected. In the mouth Cocaine abolishes the **sense of taste**, even for bitters, but sweet, salt and acid fluids can be distinguished. If applied to the nasal mucosa, it eliminates the sense of **smell.** The action of Cocaine is selective upon the sensory fibrils of mixed nerves; its selectivity is, however, dependent upon concentration, because strengths above 5 per cent. may paralyse motor, as well as sensory, conduction.

Local anæsthesia from Cocaine lasts for variable periods, depending upon the vascularity of the part. If applied to a moist mucous membrane it is soon diluted and the effect passes off in from 15 to 30 minutes, but if injected the anæsthesia may last from 1/2 an hour to 2 hours.

Cocaine **constricts the local arterioles** by sensitizing the vasoconstrictor endings to Adrenaline, therefore the part where it is applied becomes blanched. This vascular constriction prevents the rapid absorption of the Cocaine into the general circulation and serves to prolong its local anæsthetic effect.

When applied to the *conjunctiva*, Cocaine Hydrochloride solution (1 per cent.), after a momentary irritation, produces **blanching** of the conjunctiva and **anæsthesia** of the conjunctiva and cornea; and, later, an incomplete **dilatation of the pupil**, which still reacts to light; the action is due to sensitization of the sympathetic endings in the iris to Adrenaline. The anæsthetic effect on the eye lasts for about 2 hours, and, as the **winking reflex is abolished**, care must be taken to avoid entrance of dust particles.

If Cocaine were injected around the trunk of a mixed nerve, it would, by paralysing the sensory fibres, abolish the sense of pain in the whole area supplied by that nerve; this method is termed **"nerve blocking"** or **"regional anæsthesia."**

Strengths Used.—These vary with the moisture of the surface in mucous membranes. The following are employed:—For the **conjunctiva**, Cocaine Hydrochloride 1 to 2 per cent., the Lamella, 1/50 gr. or Oculentum, 0·25 per cent.; for the **mouth, nose and throat**, 5 to 10 per cent. or Lozenges containing from 1/60 to 1/20 gr.; for the **œsophagus and stomach**, 1 to 2 per cent.; for the **urethra and vagina**, 1/2 to 1 per cent. Formerly, injections of 1/2 to 1 Mil (7 to 15 min.) of a 1 to 2 per cent. solution were used locally for small operations; for **infiltration anæsthesia** to cover a wider area, 20 to 50 Mils of a 0·1 to 0·2 per cent. in 0·8 per cent. Saline Solution; and for **regional anæsthesia**, 1 Mil (15 min.) of a 1 to 2 per cent. solution.

Uses.—Cocaine is largely used in **dental practice** as a surface anæsthetic, rarely nowadays as a local injection for the removal of a tooth; it is also applied (1/6 gr.) to anæsthetize the exposed pulp prior to its removal, and to minimize the pain of arsenical dressings. In **ophthalmic surgery** and in that of the **nose and throat** it is valuable because it is the best surface anæsthetic and is rapidly absorbed. In minor general surgery Cocaine, on account of the toxic effects which may follow injections, is seldom used for regional anæsthesia, Procaine or other substitute being safer and more satisfactory.

Liquor Adrenalinæ Hydrochloridi may be applied along with Cocaine to enhance its vaso-constricting action, and thus to prolong anæsthesia and check bleeding. If Cocaine is injected, the strength of Adrenaline used should not exceed 1: 50,000 to 1: 20,000 or about 1/2 to 1 min of Liquor Adrenalinæ Hydrochloridi in 15 min. of solution. It should be noted that Cocaine and its substitutes often have little or no local anæsthetic action upon inflamed tissues, possibly because the hyperæmia dilutes them rapidly.

Cocaine Hydrochloride 1/4 gr. is added to astringent suppositories to relieve the pain of hæmorrhoids.

Internally.—Taken by mouth, Cocaine anæsthetizes the œsophagus and stomach, so that reflex vomiting can be prevented; the hunger sensation is abolished but the psychic reflex, however, remains intact and appetite is aroused by the sight of food. When Cocaine is absorbed its chief effects are exerted on the cerebrum.

Cerebrum and Medulla.—Cocaine is a **cerebral stimulant.** Small doses increase the higher cerebral functions of intellect, attention and judgment; conversation is more brilliant, decisions are made rapidly and accurately, self-confidence is exalted; fatigue is relieved and the mental and physical energies are increased; the eyes are bright and the pupils dilated. In susceptible persons or from larger doses, the motor area is particularly stimulated, and restlessness, excitement or even delirium may appear. Cocaine also **stimulates the medullary centres.** Respiration becomes quicker and deeper, and the blood-pressure is increased; in acute poisoning, by stimulation of the hypothalamus, temperature is raised.

The stage of stimulation may soon be replaced by one of **depression** and drowsiness; inco-ordinate movements, stupor and collapse supervene.

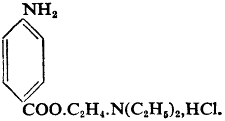
The **heart is accelerated** by Cocaine, which sensitizes the sympathetic endings to Adrenaline. The effect on the heart should be remembered, because, if Cocaine is injected with Adrenaline, palpitation, anxiety and a rapid heart beat occur in susceptible persons and an accidental intravenous injection may have fatal results. The rise of blood-pressure is partly from stimulation of the vaso-motor centre, and partly from potentiation of Adrenaline acting on the vaso-constrictor endings.

Cocainism.—The Cocaine habit is readily acquired, particularly by persons desirous of postponing natural fatigue for reasons of work or amusement. The drug is taken by injection; or as a snuff (snow), when ulceration and bleeding from the nasal mucous membrane are common. The cerebral effects, for which the drug is taken, have been described, but the addict later becomes unreliable, loses self-control, suffers from hallucinations and delusions, or fits of melancholia, and frequently becomes untruthful and immoral. Tremors of the hands and lips may appear, and also twitching or shrugging of the shoulders from a sensation of insects on the skin. A moderate tolerance is developed up to about 2 G (30 gr.) or more daily. If Cocaine is withheld from an addict, he suffers from severe mental depression and inability to concentrate; but the withdrawal symptoms are not so severe as those of Morphine.

Disadvantages of Cocaine.—The value of Cocaine as a local anæsthetic for injection is limited because: (1) its local toxicity towards tissue cells is high and, as its anæsthetic and vaso-constrictor effect passes off, there usually follows hyperæmia and œdema, causing post-operative pain and swelling in the area; (2) solutions are apt to decompose by long boiling, hence sterilization is effected by heating with a bactericide or by filtration; (3) there is a risk of developing a drug habit; (4) general toxic effects, due to idiosyncrasy, are not uncommon, thus (*a*) mental confusion and laughter, extreme motor excitement or delirium may occur from cerebral stimulation, (*b*) vomiting from medullary stimulation, (*c*) a sudden circulatory collapse, associated with anxiety, pallor of the skin, dilated pupils, dyspnœa, palpitation and rapid heart. This occurs most frequently in nervous, apprehensive patients or when Cocaine is used with Adrenaline, and is due to sympathetic stimulation. Cocaine has, however, the advantages that it is the best surface anæsthetic and itself constricts arterioles.

Excretion.—Only a small amount is destroyed in the body; the bulk is excreted unchanged in the urine within a few hours.

Procainæ Hydrochloridum.—Procaine Hydrochloride. Ethocaine. Novocain. Kerocaine. $C_{13}H_{20}N_2O_2,HCl$. The hydrochloride of *p*-amino-benzoyl-diethyl-amino-ethanol.



CHARACTERS.—Colourless crystals; odourless; taste slightly bitter followed by slight numbness. *Solubility.*—1 in 1 of water.

Dose.—(*Not official*):
Hypodermically:
Metric, up to 1 G; Imperial, up to 15 gr.
Intrathecally:
Metric, up to 0·15 G; Imperial up to 2½ gr.

Injectio Procainæ et Adrenalinæ Fortis.—Strong Injection of Procaine and Adrenaline. Procaine Hydrochloride 2, Sodium Chloride 0·5, Chlorocresol 0·1, Solution of Adrenaline Hydrochloride 2, Sodium Metabisulphite 0·1 in Water for Injection to 100.

Dose.—(*Not official*): **Metric, 1 to 4 Mils; Imperial, 15 to 60 min.**

Injectio Procainæ et Adrenalinæ Mitis.—Weak Injection of Procaine and Adrenaline. Prepared by mixing, immediately before use, "Sterile Solution of Procaine Hydrochloride," containing Procaine Hydrochloride 2, Sodium Chloride 0·8, Chlorocresol 0·1 in Water for Injection 100, with three times its volume of Injection of Sodium Chloride and adding Injection of Adrenaline in the proportion of 0·2 Mil to each 100 Mils of the Solution.

Dose.—(*Not* (*official*): *for infiltration anæsthesia:*
Metric, up to 300 Mils; Imperial, up to 10½ fl. ozs.

ACTIONS AND USES

Procaine has about one-third the general toxicity of Cocaine because it is hydrolyzed in about 20 minutes by an esterase in the liver. It has an **equal**, but less prolonged, **anæsthetic action** when injected. It is absorbed with difficulty from mucous membranes, and is, therefore, a **weak surface anæsthetic**, having only one-tenth the potency of Cocaine; it is not irritant to the tissues and does not dilate the pupil nor constrict blood-vessels: its solutions can be sterilized by boiling.

Procaine is much safer and more satisfactory for injection than Cocaine, but, as it does not constrict arterioles, it is used in combination with Adrenaline, 0·002 to 0·005 per cent., or, for infiltration anæsthesia, 0·0005 per cent. The Adrenaline, by vasoconstriction, prolongs the local action.

Procaine is a **valuable substitute for Cocaine** which it has displaced for injection purposes; when injected with Adrenaline, local anæsthesia is complete in five minutes and lasts from 1/2 an hour to 2 hours. It is used by **local hypodermic injection of**

1 Mil (15 min.) of Injectio Procainæ et Adrenalinæ Fortis, a 2 per cent. solution, for minor operations and for **regional anæsthesia** or nerve-blocking; and, by submucous or subperiosteal injection, it is employed for the painless extraction of teeth.

For **infiltration anæsthesia**, the Injectio Procainæ et Adrenalinæ Mitis, a 0·5 per cent. solution, is employed; this is used if a wider area has to be anæsthetized, when a number of injections of the Weak Solution are made around the skin area and, if necessary, gradually into the deeper tissues: to some extent the anæsthetic effect is due to the œdema caused by the fluid. With this method, or by nerve-blocking, injection of the local anæsthetic into an inflamed area can be avoided.

Spinal Anæsthesia.—If Procaine is injected intrathecally into the subarachnoid space in the lumbar region of the spinal cord, complete abolition of pain can be produced below the umbilicus, the power of movement being still retained. In the cord the action is probably exerted on the posterior nerve roots. This is the principle of intraspinal anæsthesia, which commences in 5 minutes and lasts from 1 to 2 hours. In spinal anæsthesia, loss of the sense of pain, temperature and pressure occurs, then the knee-jerk and other reflexes disappear, and the patient experiences a sensation of warmth and swelling in the limbs.

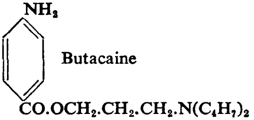
A suitable solution for this purpose is 2 to 3 Mils (30 to 45 min.) of 5 per cent. Procaine Hydrochloride in Injection of Sodium Chloride, containing 0·008 per cent. of Adrenaline Hydrochloride; the same amount of cerebro-spinal fluid being first withdrawn. Solutions above (hyperbaric) and below (hypobaric) the specific gravity (1·0068) of the cerebro-spinal fluid are made to gain a low or high action respectively. The height of the analgesia can also be modified by the level of the injection. The period of analgesia depends on the dose, 100 mg (1/6 gr.) lasting about an hour.

Spinal anæsthesia achieves complete muscular relaxation for abdominal and perineal operations; it tends to contract the intestinal muscle, however, and is not advised for perforation cases or in peritonitis. It may also be used when a general anæsthetic is undesirable, but not usually in nervous patients.

Spinal anæsthetics usually produce a considerable fall in blood-pressure and a rapid pulse; pallor, sweating and nausea are not uncommon, while dyspnœa and respiratory failure may occur. *After-effects* are not unusual, namely headache and low blood-pressure, possibly retention of urine and nervous lesions.

Procaine does not give rise to a habit, and general toxic effects are uncommon because Procaine is easily destroyed by the liver. Planocaine, Neocaine, Spinocaine and Durocaine are preparations of Procaine for spinal anæsthesia.

Butacainæ Sulphas.—Butacaine Sulphate. Butyn. The sulphate of γ-di-*n*-butylaminopropyl-*p*-amino benzoate $(C_{18}H_{30}N_2O_2)_2,H_2SO_4$.



Butacaine

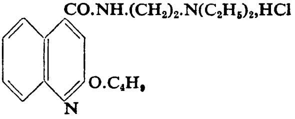
CHARACTERS.—A white, crystalline, soluble powder, taste bitter followed by numbness.

ACTIONS AND USES

Butacaine is a **good surface anæsthetic** which is easily absorbed and acts more quickly and powerfully than Cocaine; it does not dilate the pupil. When injected it causes hyperæmia. It is a useful anæsthetic in 1 to 2 per cent. solutions for ophthalmic purposes and in 2 to 5 per cent. solutions for the nose and throat. For local injections, 1 Mil (15 min.) of a 1 per cent. solution with, as it does not constrict blood-vessels, Adrenaline 0·002 per cent. may be used, but it is more toxic than Cocaine.

Cinchocainæ Hydrochloridum.—Cinchocaine Hydrochloride. Nupercaine. Percaine. The hydrochloride of β-diethylaminoethylamide of 2-butyloxycinchoninic acid.

CHARACTERS.—A white hygroscopic and soluble crystalline powder, taste bitter.



Dose.—(*Not official*): **Metric, 50 to 100 mg; Imperial, 3/4 to 1½ gr.**

ACTIONS AND USES

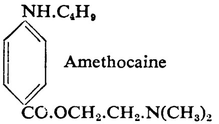
Cinchocaine has about five times greater toxicity and about ten times higher surface anæsthetic power than Cocaine but, being more slowly absorbed from mucous membranes, it is less rapid in action. When injected in equivalent strengths its effect is much more powerful and prolonged than that of Cocaine, therefore it is used in greater dilutions. It does not cause irritation nor constrict arterioles.

Cinchocaine is employed as a **surface anæsthetic** in strengths of 0·1 per cent. for the conjunctiva, 0·05 per cent. for the urethra and 1 to 2 per cent. for the nose, mouth and larynx. For **infiltration anæsthesia**, 0·02 to 0·05 per cent. solutions with Adrenaline are used; but for local injections it is regarded as too toxic without having any advantage over Procaine.

For **spinal anæsthesia**, a hypobaric (Sp. Gr. 1·0036) solution, containing 0·066 per cent., in 0·5 per cent. Sodium Chloride, is used for high analgesias, the dose being calculated from the height to which analgesia is desired; and a hyperbaric (Sp. Gr. 1·024) solution, containing 0·5 per cent. in 6 per cent. Dextrose, for low analgesias.

Over-dosage has given rise to cardiac irregularity, circulatory collapse, cyanosis, clonic convulsions and respiratory paralysis.

Amethocainæ Hydrochloridum.—Amethocaine Hydrochloride. Tetracaine. Decicain. Pantocaine. Pontocaine. Anethaine. The hydrochloride- of *p-n*-butylaminobenzoic ester of *β*-dimethylaminoethanol.



Amethocaine

CHARACTERS.—A white, crystalline, soluble powder, taste bitter followed by numbness.

Preparation

Injectio Amethocainæ Hydrochloridum.—A sterile solution, prepared immediately before use by dissolving the contents of a sealed container in Injection of Sodium Chloride.

Dose.—(*Not official*): *for spinal anæsthesia:*

Metric, 5 to 20 mg; Imperial, 1/12 to 1/3 gr.

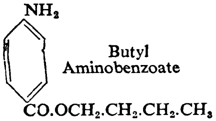
ACTIONS AND USES

Amethocaine is a powerful **surface anæsthetic** which is readily absorbed and has a more prolonged action than that of Cocaine. It is used in 1 to 2 per cent. solutions in the mouth, nose, throat and ear, in 0·25 to 1 per cent. solutions in ophthalmology, and in 0·1 per cent. solution for the urethra. A 2 per cent. ointment (Contralgin) relieves pruritus and the pain of external hæmorrhoids.

When injected it is not irritant and does not contract arterioles, therefore Adrenaline is used with it. As it is about ten times more toxic than Procaine, the solutions used are weaker. For **infiltration anæsthesia,** strengths of 0·05 to 0·1 per cent. are suitable, and for **regional anæsthesia** 1 Mil (15 min.) of a 0·2 per cent. solution gives satisfactory analgesia.

For **spinal anæsthesia**, a hypobaric solution contains 0·066 per cent. in 0·5 per cent. Sodium Chloride; a hyperbaric solution is 0·5 per cent., or the required dose, in 6·3 per cent. Dextrose.

Butylis Aminobenzoas.—Butyl Aminobenzoate. Butesin. Scuroform. *n*-butyl-*p*-aminobenzoate.



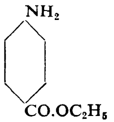
CHARACTERS.—A white, crystalline, tasteless powder. *Solubility.*—1 in 7,000 of water, soluble in fixed oils.

ACTIONS AND USES

Butyl Aminobenzoate is a **surface anæsthetic** which, being almost insoluble, has a prolonged action. It is used as a **dusting powder**, sometimes diluted with Boric Acid, on ulcers and surface wounds or burns to relieve pain. It is also applied in ointments or in oily solution, or in suppositories to relieve pain from hæmorrhoids and fissure of the anus or itching in pruritus.

Benzocaina.—Benzocaine. Anæsthesine. Ethyl *p*-aminobenzoate.

CHARACTERS.—A white, crystalline powder; odourless; taste bitter, succeeded by numbness. *Solubility.*—1 in 2,500 of water, 1 in 8 of alcohol, 1 in 50 of fixed oils.

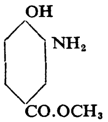


ACTIONS AND USES

Benzocaine is a **surface anæsthetic.** Being almost insoluble, it is used mainly as a **dusting powder** for burns, pruritus, itching skin diseases and for cancerous ulcers. Solutions, 2 per cent. in Olive Oil or dilute Alcohol, may be used as paints or sprays for mucous membranes. As an ointment (10 per cent.) or in suppositories (10 gr.), it is used for anal fissure and piles.

Internally.—It is given to relieve the pain of gastric ulcer and carcinoma.

Orthocaina.—Orthocaine. Orthoform. The methyl ester of *m*-amino-*p*-hydroxybenzoic acid.



CHARACTERS.—A white or yellowish crystalline powder; odourless; tasteless. *Solubility.*—Sparingly in water; 1 in 7 of alcohol.

ACTIONS AND USES

Orthocaine is a **surface anæsthetic** used as a dusting powder, diluted if necessary, to relieve pain in wounds, ulcers and burns. Bougies containing 5 per cent. in Oil of Theobroma are useful in urethral irritation.

Internally it is employed in gastric ulceration and, by insufflation, in laryngeal tuberculosis.

Lignocaine.—Xylocaine. ω-diethylamino-2 : 6-dimethylacetanilide.

CHARACTERS.—Available in 20-Mil phials containing Xylocaine Hydrochloride 2%, Adrenaline 0·002%, Sodium Chloride 0·6%, Sodium Pyrosulphite 0·05% and Methylparaoxybenzoate 0·1%.

ACTIONS AND USES

Xylocaine is a satisfactory local anæsthetic for both surface and injection purposes; its solutions can be boiled and it is not irritant. It is unrelated chemically to other local anæsthetics. For surface anæsthesia, 2 per cent. solutions containing Adrenaline act within 2 to 3 minutes on mucous surfaces. For injection, a 2 per cent. solution with 0·001 to 0·002 per cent of Adrenaline in dose of 1 to 2 Mils gives a rapid and effective local anæsthesia lasting about 1½ hours and with a wider area than Procaine produces; recovery occurs in about 2 to 4 hours. Side- or after-effects are very rare.

Benzaminæ Lactas (B.P.C.).—β-Eucaine. The lactate of trimethyl benzoyloxypiperidine $C_{15}H_{21}NO_2$.

CHARACTERS.—A white, crystalline powder; taste slightly bitter, followed by numbness. *Solubility.*—1 in 5 of water; 1 in 8 of alcohol 90%.

Dose.—Metric, 8 to 30 mg; Imperial, 1/8 to 1/2 gr.

ACTIONS AND USES

Benzamine Lactate is a **local anæsthetic** acting like Cocaine; in comparison, it has one half the general toxicity and anæsthetic power of Cocaine: its action is slower and weaker. It is not readily absorbed by mucous membranes, and therefore has one-quarter the value of Cocaine as a surface anæsthetic; it is slightly irritant, does not constrict blood-vessels nor dilate the pupil, but often causes hyperæmia. Solutions varying from 2 to 5 per cent. are sometimes used for the same purposes as Cocaine. For infiltration anæsthesia 0·1 per cent. solutions are used in 0·8 per cent. Saline. It is best combined with Adrenaline (1: 50,000).

Tropacocainæ Hydrochloridum (*not official*).—Benzoyl-pseudo-tropine. $(CH_2)_2.C_5H_7(CH_3)N.O.CO.C_6H_5,HCl$. Colourless, soluble, needle-like crystals.

ACTIONS AND USES

Tropacocaine has one-half the surface anæsthetic value and toxicity of Cocaine but an almost equal, although less prolonged, anæsthetic effect when injected. It is, however, irritant and does not constrict blood-vessels, nor dilate the pupil. For local anæsthesia, 3 to 5 per cent. solutions have been used.

Amylocainæ Hydrochloridum (B.P.C.).—Amylocaine Hydrochloride. Stovaine. $C_{14}H_{21}NO_2,HCl$. The hydrochloride of the benzoyl ester of methyl-ethyl-dimethyl-aminomethyl carbinol.

CHARACTERS.—Colourless crystals; taste bitter followed by transient numbness. *Solubility.*—1 in 2 of water.

Dose.—*Orally and hypodermically:*

Metric, 20 to 50 mg; Imperial, 1/3 to 3/4 gr.

Intrathecally:

Metric, 20 to 60 mg; Imperial, 1/3 to 1 gr.

ACTIONS AND USES

Amylocaine has a weak surface anæsthetic value and when injected is more toxic and a slightly stronger local anæsthetic than Procaine. It is irritant to the tissues, causing hyperæmia, and does not constrict blood-vessels or dilate the pupil.

Its main use is for **intrathecal anæsthesia**: 1 to 2 Mils of a 5 per cent. Amylocaine (i.e. 0·05 to 0·1 G) in 5 per cent. Glucose Solution is injected after allowing 5 to 10 Mils of cerebro-spinal fluid to escape. Anæsthesia is complete in about 10 minutes and lasts about an hour; it frequently abolishes motor power as well as sensation. *Toxic symptoms* in the form of after-effects, such as headache, nausea and syncope from reduced blood-pressure, are fairly common.

Procaine Borate.—Borocaine. Ethocaine Borate. $(C_{13}H_{20}N_2O_2)_2,4H_2O.,5B_2O_3$. A white crystalline powder.

Dose.—1 Mil of a 2 to 5% solution with Adrenaline.

ACTIONS AND USES

It has one-twentieth the surface anæsthetic value of Cocaine and, when injected, one-half the anæsthetic power of Cocaine or Procaine. It is not irritant and does not constrict blood-vessels.

Other substitutes for Cocaine are *Holocaine* (phenocain), amydricaine (*Alypin*), *Psicaine* and *Tutocaine* but none of these possesses unusual advantages. Quinine and Urea Hydrochloride is also a local anæsthetic (*see* p. 361).

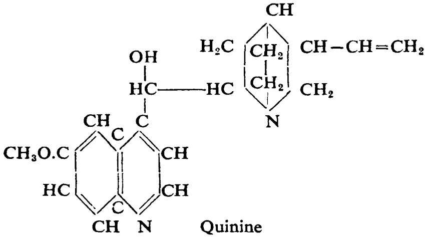
ANTIPYRETICS

These are drugs or measures which reduce febrile temperature. They may act (1) by external cooling, e.g. tepid sponging, wet packs; (2) by depressing the heat-regulating centre in the hypothalamus, e.g. Salicylates, Phenacetin, etc.; (3) by increasing the heat loss through dilatation of the cutaneous vessels and increased perspiration, e.g. Alcohol, Nitrites, Ipecacuanha, and (but not so used) Pilocarpine; (4) by toxic action on causal organisms, e.g.

Quinine in malaria, Salicylates in acute rheumatism and Sulphonamides, Penicillin and other antibiotics in various infections.

Quininæ Sulphas.—Quinine Sulphate. $(C_{20}H_{24}N_2O_2)_2H_2SO_4,2H_2O$. The sulphate of an alkaloid, Quinine, obtained from the bark of various species of Cinchona. N.O. Rubiaceæ.

CHARACTERS.—Colourless, silky needles; efflorescent; no odour; taste intensely bitter. *Solubility.*—1 in 800 of water, imparting to it a fluorescent blue; entirely in water acidulated with a mineral acid. In mixtures, 1 min. of dilute mineral acid dissolves one grain. Aqueous solutions give with Br water and then a drop of NH_4OH a green colour (Thalleioquin Test).
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.



Quinine

Quininæ Bisulphas.—Quinine Acid Sulphate. $C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$. The bisulphate of the alkaloid Quinine.

CHARACTERS.—Colourless, small needles; odourless; taste very bitter; efflorescent and turns yellow in light. *Solubility.*—1 in 10 of water; solution *acid.*
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparation

Tabellæ Quininæ Bisulphatis.—0·3 G (5 gr.) in each.

Quininæ Hydrochloridum.—Quinine Hydrochloride. $C_{20}H_{24}N_2O_2,HCl, 2H_2O$. The hydrochloride of the alkaloid Quinine.

CHARACTERS.—White, silky crystals, efflorescent in warm air; odourless, taste very bitter. *Solubility.*—1 in 32 of water; solution *neutral.*
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparations

1. **Tabellæ Quininæ Hydrochloridi.**—0·3 G (5 gr.) in each.
2. **Injectio Quininæ et Urethani.**—Injection of Quinine and Urethane. Quinine Hydrochloride 12·5, Urethane 6·25 in Water for Injection to 100.
Dose.—*By intravenous injection as a sclerosing agent:*
Metric, 0·5 to 5 Mils; Imperial, 8 to 75 min.

Quininæ Dihydrochloridum.—Quinine Acid Hydrochloride. $C_{20}H_{24}N_2O_2, 2HCl$. The dihydrochloride of the alkaloid, Quinine.

CHARACTERS.—A white amorphous powder; odourless; taste very bitter. *Solubility.*—1 in 0·6 of water; solution *acid.*

Dose.—*Orally:*

Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

By intravenous injection:

Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparation

Injectio Quininæ Dihydrochloridi.—A sterile solution for intravenous use in Water for Injection. Contains 0·3 G (5 gr.) in 5 Mils (75 min.) but a solution of this strength must be first diluted with at least 10 times its volume of Injection of Sodium Chloride and be injected slowly.

Quininæ et Æthylis Carbonas.—Quinine Ethyl Carbonate. Euquinine $C_{20}H_{23}N_2O_2.CO_2.C_2H_5$.

CHARACTERS.—White, soft needles; odourless; almost tasteless; darkening in light. *Solubility.*—Slightly in water; readily in dilute acids.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Totaquina.—Totaquine. A mixture of the alkaloids from the bark of Cinchona. N.O. Rubiaceae. Contains 70% of alkaloids of which 14% is Quinine.

CHARACTERS.—A colourless or yellowish-brown powder; odourless; taste bitter. *Solubility.*—Almost insoluble in water; soluble in warm alcohol.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

Quinine is a **protoplasmic poison**; it is particularly toxic to leucocytes and protozoa (1:10,000) but less so to bacteria (1: 500); it is, therefore, an **antiseptic** although not used for this purpose. When applied to raw surfaces or injected, the soluble salts in solutions above 0·25 per cent. are at first irritant and then paralyse the sensory fibrils, so that Quinine acts as a **local anæsthetic,** the duration of the effect being longer than that of Cocaine. Local necrosis of the tissues may occur if solutions of Quinine salts are injected hypodermically or intramuscularly.

Solutions of Quinine Hydrochloride, 5 to 12 per cent., with Urethane, 3 to 6 per cent., are injected in amounts of 1/2 to 5 Mils into **varicose veins** to cause sclerosis by irritation of the endothelium; similar injections are made superficial to the veins to sclerose hæmorrhoids.

Internally.—Soluble Quinine salts are readily absorbed by mucous membranes. In the *mouth* they are **bitters** and reflexly increase the salivary and gastric secretions (*see* p. 158).

In the *stomach* large doses of Quinine salts inhibit the action of enzymes, are irritant and may cause nausea.

Absorption of Quinine Salts.—The soluble Bisulphate and the Hydrochlorides are quickly absorbed from the small intestine, as is also the Sulphate, provided it is given in solution with acid but, if it is given as pills or tablets, a very small amount is absorbed. Quinine Ethyl Carbonate is less bitter and more slowly absorbed; it is used for children.

Actions after Absorption.—Blood: Quinine salts increase the number of lymphocytes in the circulation by contracting the plain muscle of the spleen. After repeated doses, the numbers of all leucocytes decrease but this phase may be followed by a leucocytosis.

Circulatory and Respiratory Systems.—In man, small doses of Quinine sometimes cause a slight acceleration of the pulse. Large doses weaken the heart muscle and relax the arterioles, producing flushing of the skin, sweating and a **fall in blood-pressure**. This circulatory depressant action is considerable from intravenous injection of the Dihydrochloride, which must be given well-diluted and very slowly. Respiration is not influenced except by toxic doses, which stimulate and later depress the centre.

Central Nervous System.—Large doses of Quinine—or even small doses in susceptible persons—produce a complex of symptoms termed **Quinism** or **Cinchonism**; these are headache, ringing in the ears leading to deafness, some impairment of vision, muscular weakness with uncertain gait and, less commonly, skin eruptions of urticarial, papular or purpuric type. The **aural symptoms** have been ascribed to congestion of the tympanum and to degenerative changes in the spiral ganglion of the cochlea. The *ocular symptoms* consist in dilated pupils, obscured vision, contraction in the visual field or colour field (quinine amblyopia) or blindness, which may recover only slowly. The retina is found to be anæmic and the optic disc pale, probably from spasm of the retinal arteries. Symptoms of quinism may to some extent be averted by giving Bromides along with the Quinine. Quinine Hydrochloride, 10 gr. daily, relieves myotonia congenita and atrophica.

Involuntary Muscles.—Quinine salts **stimulate uterine muscle**. The parturient uterus becomes more sensitive to Quinine as full term approaches. Quinine will not induce premature labour but it is a valuable means at full term of **exciting labour** and of augmenting weak contractions during the first stage. Although increasing the rhythmic movements, it does not cause a powerful tone; therefore there is no danger to the cervix or fœtus. In practice three doses of 0·6 G (10 gr.) of Quinine Hydrochloride are given at hourly intervals; this produces a peak of Quinine concentration in the blood between the 6th and 12th hour afterwards. Some of the Quinine passes into the fœtus but is not injurious.

Temperature.—Quinine is an **antipyretic**; it diminishes heat production and increases heat loss by direct depression of the thermogenetic centre in the hypothalamus, and by dilatation of the superficial vessels. Quinine has little or no effect on a normal temperature. In fevers, its action is unreliable but it is frequently prescribed for influenzal and catarrhal colds, usually together with salicylates.

Quinine in Malaria.—The chief value of Quinine is as a **suppressive for malaria**, a disease due to one of three parasites: Plasmodium vivax (benign tertian fever), P. malariæ (benign quartan fever) and P. falciparum (malignant tertian fever). The fever in man recurs each time the asexual spores (trophozoites or merozoites) are liberated from the sporulating schizonts in the corpuscles; that is, every third (tertian) or fourth (quartan) day.

The life-cycle of the malarial parasite is briefly that the sporozoites injected by the female mosquito develop into exo-erythrocytic (E.E.) forms in the liver cells, and then into the intracorpuscular schizonts which sporulate asexually to form the trophozoites or merozoites; gametocytes are formed in human blood but undergo sexual development only after entering the body of a mosquito. The schizonts (asexual forms) only are eradicated by Quinine, Mepacrine and Chloroquine; both the exo-erythrocytic and asexual forms appear to be destroyed by Proguanil (Paludrine); while Pamaquin is particularly toxic to the gametocytes.

Quinine is a **schizonticide**, i.e. it destroys the asexual cycle, and, therefore, is properly described as a **suppressive agent**; it has no action on the sporozoites or on the exo-erythrocytic forms, and is, therefore, not a causal prophylactic; and, as it is not toxic to the gametocytes, it does not prevent infection of healthy persons through mosquitoes which have bitten gametocyte carriers.

Although not a causal prophylactic, Quinine is useful as a **prophylactic suppressive.** Tablets of Quinine Bisulphate or Hydrochloride are rapidly absorbed, and, for prophylaxis, a daily dose of 0·6 G (10 gr.) should be commenced the day before entering, and maintained for a month after leaving, an infected area.

Mepacrine, which less frequently causes undesirable symptoms, is, however, commonly preferred.

Clinically, as soon as malaria is diagnosed, Quinine in dosage of 1·2 to 2 G (20 to 30 gr.) should be given by mouth daily for 5 or 7 days, that is, until two expected attacks are aborted and the temperature remains normal. In **treating benign fevers** Quinine Hydrochloride, Dihydrochloride, Bisulphate or the Sulphate in acid solution, is given in 0·6 G (10 gr.) doses thrice daily for a week. Then a dose of 10 gr. daily should be maintained for 2 or 3 months. In **malignant tertian cases** 10 gr. every 4 hours may be necessary until cerebral symptoms and temperature abate, or, if the case becomes serious or comatose, intravenous injection of 0·6 G (10 gr.) of Quinine Dihydrochloride, dissolved in 20 to 100 Mils of Injection of Sodium Chloride, should be given very slowly so as to avoid a severe fall of blood-pressure or cardiac failure. Intravenous dosage produces a rapid action but the blood concentration soon falls to the level obtainable from oral administration and, as it causes severe quinism and possibly circulatory collapse, intravenous dosage is usually given as a last resort in serious cases.

For **children**, doses proportional to body weight are used, and for them the almost tasteless Quinine Ethyl Carbonate is suitable although, as it has to be hydrolyzed by the gastric acid, it is less completely absorbed. Totaquina, as it is much less expensive, may be employed for the mass treatment of communities and the poorer classes, but it is less useful for P. falciparum infections.

Excretion of Quinine.—About 80 per cent. of the Quinine administered is destroyed in the body; excretion of the remainder by the kidney commences in an hour, reaches a peak in from 6 to 12 hours, and is small after 24 hours. During excretion, Quinine may irritate the kidney and large doses can cause albuminuria; hæmaturia may occur during the treatment of malaria. Quinine pessaries (3 to 5 gr.) are unreliable contraceptives.

Mepacrinæ Hydrochloridum.—Mepacrine Hydrochloride. Quinacrine. Atebrin. The dihydrochloride of 2-chloro-5-(ω-diethylamino-α-methylbutylamino)-7-methyoxyacridine. $C_{23}H_{30}N_3OCl,2HCl,2H_2O$.

CHARACTERS.—A yellow, crystalline powder, taste bitter. *Solubility.*—1 in 40 of water.

Dose.—*Prophylactic daily:*

Metric, 0·1 G; Imperial, 1½ gr.

Therapeutic daily in divided doses:

Metric, 0·2 to 0·5 G; Imperial, 3 to 8 gr.

Preparation

Tabellæ Mepacrinæ Hydrochloridi.—0·1 G ($1\frac{1}{2}$ gr.) in each.

Mepacrinæ Methanosulphonas.—Mepacrine Methanesulphonate. Atebrin Musonate. $C_{23}H_{30}N_3OCl,2CH_3SO_3H,H_2O$.

CHARACTERS.—A yellow, crystalline solid, taste bitter. *Solubility.*—1 in 3 of water.

Dose.—*By intramuscular injection:*
Metric, 0·1 to 0·3 G; Imperial, $1\frac{1}{2}$ to 5 gr.

Preparation

Injectio Mepacrine Methanosulphonatis.—A sterile solution for intramuscular injection, prepared by dissolving, immediately before use, the contents of a sealed container in the required amount of Water for Injection.

ACTIONS AND USES

Mepacrine is a **schizonticide**, that is, it destroys the asexual cycle of the malarial parasite; but it has no action on the sporozoites, tissue forms or gametocytes. It is, therefore, a **suppressive agent**, but it is better tolerated and less toxic than Quinine; it is equally effective in benign tertian and quartan fevers and usually more effective in malignant tertian fever than Quinine.

After a week's dosage, Mepacrine colours the skin yellow and this lasts for two or three weeks after treatment stops. With small daily doses, the plasma concentration rises slowly, but, as the drug is slowly excreted by the urine, which becomes bright yellow, it may by cumulation give rise to headache, nausea, vomiting, gastric pain, and mental disturbances, although these are not usually serious. The nausea may be overcome by giving Mepacrine well diluted and with Sodium Bicarbonate.

As a **prophylactic suppressive,** doses of 0·1 G ($1\frac{1}{2}$ gr.) daily should, for the above reason, be started three weeks before entering a malarial region, and maintained for a month after leaving.

For **treatment**, it is desirable to attain rapidly a high plasma concentration, and four or five doses of 0·2 G (3 gr.), followed by four doses of 0·15 G ($2\frac{1}{4}$ gr.), are given at 6-hourly intervals, and then 0·1 G ($1\frac{1}{2}$ gr.) thrice daily for 5 or 6 days. In serious cases, Mepacrine Methanesulphonate is given by intramuscular injection in dose of 0·2 G (3 gr.) in 5 or 10 Mils of Water for Injection; this may be repeated, if necessary, in 6 hours, and followed by oral administration.

Mepacrine is usually curative in malignant tertian malaria, although relapses are to be anticipated in benign tertian malaria; these are treated similarly when they arise but with somewhat smaller dosage. Relapses of malignant tertian infections are best treated by Mepacrine because Quinine may cause hæmaturia (blackwater fever). Mepacrine should not be given along with Pamaquin. Mepacrine is usually an effective treatment for giardiasis.

Pamaquinum.—Pamaquin. Plasmoquine. Præquin. Aminoquin. 6-methyoxy-8-(ω-diethylamino-α-ethylbutyl)-aminoquinoline salt of 2 : 2′-dihydroxy-1 : 1′-dinaphthylmethane-3 : 3′-dicarboxylic acid. $C_{42}H_{45}N_3O_7$.

CHARACTERS.—An orange-yellow, insoluble powder, taste bitter.

Dose.—Metric, 10 to 20 Mg; Imperial, 1/6 to 1/3 gr.

ACTIONS AND USES

Pamaquin is only moderately effective against the asexual parasites, i.e. is a weak schizonticide, but is **toxic to the gametocytes** in human blood, therefore it is used after suppressive treatment with Quinine or Mepacrine to eradicate gametocytes and so prevent the patient from infecting mosquitoes; it also reduces the relapse rate in P. vivax infections.

Pamaquin has a small safety margin, and is slowly excreted; large doses can cause serious toxic effects; headache, giddiness, nausea, vomiting, jaundice and severe epigastric pain are common, while methæmoglobinæmia with cyanosis, hæmolytic anæmia with hæmaturia and agranulocytosis may also occur. Pamaquin is partly detoxicated in the body, but Mepacrine interferes with this and thus increases the plasma concentration, and, therefore, the toxicity of Pamaquin; hence the two drugs must not be given together.

Pamaquin is given orally in dose of 20 mg (1/3 gr.) thrice daily for five days usually during the week following Quinine or Mepacrine treatment.

Pentaquine Diphosphate.—*Dose*: 60 mg daily, acts like Pamaquin and is less toxic.

Chloroquine Diphosphate.—7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline.

Dose.—*Suppressive:*
Metric, 0·3 G; Imperial, 5 gr. in tablets.
Therapeutic, daily for five days:
Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

Chloroquine has three times the potency of Mepacrine or Quinine as a **schizonticide**, thus a single weekly dose is sufficient as a suppressive prophylactic, while for treatment it is effective within five days and lengthens the intervals between relapses. Chloroquine does not discolour the skin, nor cause gastro-intestinal symptoms as a rule.

Proguanilum Hydrochloridum (B.P.C.).—Paludrine. The hydrochloride of N^1-*p*-chlorophenyl-N^5-*iso*propyl-diguanide.

CHARACTERS.—A white, crystalline powder; taste bitter. *Solubility.*—1 in 80 of water.

Dose.—*Orally, daily:*

Metric, 0·1 to 0·4 G; Imperial, 1½ to 6 gr.

ACTIONS AND USES

Proguanil is a **schizonticide**, but is also toxic to the exo-erythrocytic tissue forms, particularly of P. falciparum, hence for malignant tertian malaria it is not only a **suppressive agent** but also a **causal prophylactic** and a curative agent. It is a suppressive for P. vivax infections, but is a less effective toxic agent for the latent tissues forms, therefore cases of benign tertian malaria may relapse. It is not a gametocide, but its presence in the blood of a gametocyte carrier prevents the development of the gametocytes in a mosquito, thus it renders the carrier non-infectious. Proguanil is readily absorbed but is slowly excreted in the urine during about nine days, so that a weekly dose of 0·3 G can maintain an adequate blood concentration of between 0·01 and 0·1 mg per cent.

As a prophylactic suppressive for all types of malaria in endemic areas, the daily dose of Proguanil should be 0·1 G (1½ gr.); or, for children from birth to five years, 25 mg (2/5 gr.), and from six to twelve years, 50 mg (3/4 gr.). As an alternative, 0·3 G (5 gr.) should be taken on the same day each week (children proportionately less).

As a therapeutic agent for malignant tertain malaria, Proguanil is given in doses of 0·3 G (5 gr.) twice daily for 10 days, and then in 0·1 G (1½ gr.) doses daily for 6 weeks; but, as its action starts slowly, Mepacrine is usually given also on the first day of treatment. For benign tertian infections, 0·1 G (1½ gr.) of Proguanil with 10 mg (1/6 gr.) of Pamaquin is advised thrice daily for 10 days, if the patient can be treated in bed; if not, 0·1 G (1½ gr.) of Proguanil alone is given thrice daily for 10 days and followed by 0·3 G (5 gr.) on the same day each week for a year to obviate relapses.

Toxic effects from Proguanil are rare; excessive doses may cause vomiting, and prophylactic doses may cause loss of appetite and weight.

Quinine and Urea Hydrochloride.—A white, odourless powder. *Solubility.*—1 in 1 of water; solution acid.

Dose.—*Subcutaneously or intramuscularly:*
Metric, 0·03 to 1 G; Imperial 1/2 to 15 gr.

ACTIONS AND USES

This salt is **antiseptic** and also a **local anæsthetic** by paralysing sensory fibrils like Cocaine. In 2 per cent. solution it has about one-quarter the surface anæsthetic value of Cocaine and one-eighth of its power for nerve-blocking, but the effects last 6 or more hours. It is at first irritant, and its toxicity on cells may cause local necrosis.

Quinine and Urea Hydrochloride is used in strengths of 1 to 2 per cent. as an **anodyne antiseptic** for wounds and ulcers, its prolonged use delays healing; for mucous membranes 10 to 20 per cent. solutions are analgesic; in ointments (20 per cent.) or suppositories (5 gr.) it is used for piles; and 1 Mil of a 0·25 to 1 per cent. solution is employed for regional anæsthesia. A 5 to 10 per cent. solution is injected in the submucosa to cause sclerosis in hæmorrhoids.

In **malaria**, intramuscular injections of 1 G (15 gr.) in 5 to 10 Mils of Saline Solution are used as they are somewhat less painful than the Dihydrochloride.

Chiniofonum.—Chiniofon.—Yatren. Quinoxyl. A mixture of about four parts by weight of 7-iodo-8-hydroxy-quinoline-5-sulphonic acid and one part by weight of Sodium Bicarbonate.

CHARACTERS.—A light-yellow powder; odourless, taste bitter, later sweet. *Solubility,* 1 in 25 of water.

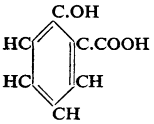
Doses.—Metric, 0·06 to 0·5 G; Imperial, 1 to 8 gr.
By rectal injection:
Metric, 1 to 5 G; Imperial, 15 to 75 gr.

ACTIONS AND USES

Chiniofon is valuable in the treatment of acute and chronic **amœbic dysentery,** for which it is given as tablets in doses of 4 gr. increasing to 8 gr. three times daily after meals for a week, and dosage repeated on two or three days in the following two weeks. In addition, when the case is an acute one, enemata of 200 Mils (6 fl. oz.) of a 2 per cent. solution at body temperature should be given each evening until the fluid is retained.

ANALGESIC OR ANODYNE ANTIPYRETICS

Acidum Salicylicum.—Salicylic Acid. $C_6H_4.OH.COOH$.



CHARACTERS.—Colourless, prismatic crystals; odourless; taste sweet, then acrid. *Solubility.*—1 in 500 of water; 1 in 3·5 of alcohol 90%; 1 in 2 of ether; dissolves in solutions of ammonium citrate, acetate, and of sodium phosphate. Solutions give a violet colour with Fe_2Cl_6 solutions.

Preparations

1. **Unguentum Acidi Salicylici.**—Salicylic Acid, 2% in Ointment of Wool Alcohols.
2. **Bismuthi Salicylas.**—Bismuth Salicylate. *See* p. 64.

Sodii Salicylas.—Sodium Salicylate. $C_6H_4.OH.COONa$.

CHARACTERS.—Small colourless scales, or tabular, pearly crystals; inodorous; taste sweetish, unpleasant, saline. *Solubility.*—1 in 1 of water, but this may deposit crystals of the hexahydrate; solutions neutral or faintly acid. Solutions give violet colour with Fe_2Cl_6 solutions.

Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

Preparation

Tabellæ Sodii Salicylatis.—0·3 G (5 gr.) in each; they should be dissolved in water before administration.

ACTIONS AND USES

Externally.—Salicylic Acid acts as an **antiseptic** in saturated (0·2 per cent.) solutions; it is less likely to cause necrosis than Phenol. It is occasionally used as a surgical dressing in the form of cotton-wool or gauze impregnated (4 per cent.) with the Acid. Salicylic Acid (3 per cent.) in powder, diluted with talc, is an **anhidrotic**, checking local perspiration. Strong solutions (10 to 20 per cent.) of the Acid in acetone-collodion or rubber plaster are **caustic**; they cause necrosis of horny epidermis, which softens and separates without scarring, and they are employed to remove corns and warts. The ointment is useful in treating acne, eczema, ringworm, urticaria, pityriasis, chilblains and indolent ulcers.

Internally.—In the stomach, Salicylic Acid is irritant and reflexly causes nausea and vomiting. Bismuth Salicylate, which is a mechanical sedative and, by liberating Salicylic Acid in the intestine, a slight antiseptic, is used to treat diarrhœa. Sodium Salicylate is **slightly irritant** because some Salicylic Acid is dissociated from it by the gastric acid, but this may be minimized by prescribing **Sodium Salicylate with equal doses of Sodium Bicarbonate.**

Absorption of Salicylates and Salicylism.—Salicylates are absorbed rapidly from the small intestine. Moderate doses produce effects which resemble quinism, namely, fullness in the head, headache or vertigo with some mental confusion, nausea and vomiting, ringing in the ears and dullness of hearing, impairment of vision, flushing and warmth of the skin with free perspiration, increased rapidity of the heart and accelerated or deepened respiration.

The initial symptoms, headache, etc., are cortical in origin; the tinnitus may be due to aural congestion; the delayed vomiting is due to medullary stimulation and the increased rapidity of the heart is probably of sinus origin. The dilatation of the cutaneous vessels and sweating result from an action on the thermogenetic centre. Large doses of Salicylates lower the prothrombin content of the blood.

These effects are not serious and subside if the dose be reduced. They resemble the symptoms of acidosis and may to some extent be prevented by giving Salicylates along with Sodium Bicarbonate.

In normal persons, therapeutic doses of Salicylates produce no other important effects; they do not reduce normal temperature nor depress the heart. They augment nitrogenous metabolism to a slight degree and the excretion of urea, uric acid and sulphur rises, but the increase in uric acid is due to a lowering of the renal threshold for this substance. Sodium Salicylate is, therefore, of value in treating chronic gout or the uric acid diathesis and is much safer than Cinchophen. Sodium Salicylate also increases slightly the secretion of bile.

Antipyretic Action.—Salicylates are **powerful antipyretics,** lowering the temperature in fever very effectively, although they do not lower the temperature in health. They act by lowering the point of thermal equilibrium through a depressant action on the thermogenetic centre in the hypothalamus. The fall in temperature is due to augmented loss of heat from cutaneous vascular dilatation and increased perspiration.

Sodium Salicylate is employed in two distinct classes of cases: (1) In pyrexia from any cause, such as influenza, pneumonia, pyæmia, etc., it is a useful antipyretic; it is rapid in action, and probably exerts some antiseptic effect on the organisms causing the fever. In influenza it also relieves muscular pain. (2) In **acute rheumatism** Sodium Salicylate is a specific; it reduces the temperature, relieves the pain, redness and swelling of the joints and other local symptoms within two to five days and shortens the duration of the disease. By thus curtailing the course of rheumatism, it may indirectly reduce the liability to cardiac and other complications, although it cannot be relied upon to prevent these. Sodium Salicylate, being rapidly excreted, should be given at first in large doses, 20 to 30 gr. every 2 to 4 hours in combination with equal amounts of Sodium Bicarbonate to prevent the formation of Salicylic Acid in the stomach. When the temperature is normal, 10 to 15 gr. should be given every four hours for two or three weeks, and the dose must be reduced gradually, because relapses are frequent owing to sudden discontinuance. Children tolerate Sodium Salicylate, even 200 gr. daily, well and will accept it if the flavouring is changed from time to time.

Sodium Salicylate has moderate analgesic effects in subacute, muscular and chronic rheumatism. Occasionally it affords relief in sciatica, arthritis and acute gout.

Excretion.—The excretion of Salicylates is rapid; it commences in 15 minutes and is completed within 12 to 24 hours. The bulk (75 per cent.) is eliminated by the kidney in the form of Salicylates, although a portion is oxidized to oxysalicylic acid and some is combined with glycuronic acid; traces are excreted in the salivary, gastric and sweat secretion. Salicylates are weak diuretics and urinary antiseptics.

Salol (*not official*).—Phenyl Salicylate. $C_6H_4.OH.COO.C_6H_5$.

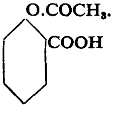
CHARACTERS.—Colourless crystals; odour aromatic; taste slight *Solubility.*—Almost insoluble in water.

Dose.—Metric, 0·3 to 1·2 G; Imperial, 5 to 20 gr.

ACTIONS AND USES

This compound of Salicylic Acid and Phenol is split into its components by lipase in the duodenum. Since it is not decomposed in the stomach, it is used to coat pills intended to be dissolved in the intestine and to diagnose pyloric obstruction by the time of excretion of Salicylates (normal 15 to 30 min.), in the saliva or urine. Its components are weak **intestinal antiseptics**, and it was formerly prescribed for intestinal infections without material benefit.

Acidum Acetylsalicylicum.—Acetylsalicylic Acid. "Aspirin." $CH_3.CO_2.C_6H_4.COOH$.



CHARACTERS.—A white, crystalline, inodorous powder; taste slightly acid. *Solubility.*—1 in 300 of water, solution acid; 1 in 5 of alcohol 90%. Boiled with NaOH and neutralized by dilute H_2SO_4, salicylic and acetic acids are formed. Aqueous solutions, boiled, give a violet-red colour with Fe_2Cl_6 solution.

Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

Preparations

1. **Tabellæ Acidi Acetylsalicylici.**—0·3 G (5 gr.) in each.
2. **Tabellæ Acidi Acetylsalicylici cum Ipecacuanha et Opio.**—0·162 G (2½ gr.) each of Aspirin and Dover's Powder. *Dose.*—1 or 2 tablets.
3. **Tabellæ Acidi Acetylsalicylici et Phenacetini.**—0·2268 G (3½ gr.) of Aspirin and 0·162 G (2½ gr.) of Phenacetin in each. *Dose.*—1 or 2 tablets.
4. **Tabellæ Codeinæ Compositæ.**—0·2592 G (4 gr.) of Aspirin and Phenacetin, and 8·1 mg (1/8 gr.) of Codeine Phosphate in each. *Dose.*—1 or 2 tablets.

ACTIONS AND USES

Acetylsalicylic Acid has usually only a slight irritant effect on the stomach, but large doses may cause gastritis and hæmorrhage. In the duodenum it is partly converted to salicylates, but the bulk is absorbed rapidly as sodium acetylsalicylate. It acts as an **antipyretic** by depressing the thermogenetic centre, and thus lowers the point of thermal equilibrium in fevers. Its effects are more rapid than those of Sodium Salicylate, and in doses of 10 gr. it produces free perspiration within an hour. Aspirin does not produce salicylism, but over-dosage, or idiosyncrasy to it, may cause urticaria, itching, or œdema of the skin, particularly in the facial area.

Acetylsalicylic Acid is less effective than Sodium Salicylate in acute rheumatism, but it is a valuable antipyretic in influenzal, catarrhal or infectious fevers and in subacute rheumatism. Its more important value depends upon the fact that, without impairing the cerebral functions, it relieves moderate pain by depressing the thalamic cell station on the path of the pain fibres; therefore it is used as an **anodyne** or analgesic in a variety of painful conditions, such as wounds, nervous headache, myalgia, migraine, trigeminal neuralgia, dental caries and pulpitis, articular rheumatism, osteo-arthritis, tabes, and gout. By its analgesic effect, it is often useful to facilitate sleep in these complaints. In gout, it increases the excretion of uric acid. It is best given in tablet form. The compound tablets with Dover's Powder are useful antipyretics for febrile colds; the tablets of Aspirin and Phenacetin are useful analgesics without a cerebral depressant effect. Tabellæ Codeinæ Co. resemble Veganin and are analgesics both by the thalamic action of the Aspirin and Phenacetin, and by the cerebral action of Codeine; they are largely used to relieve pain and promote sleep.

Veganin (1 to 2 tabs.) is Acetylsalicylic Acid 3¾ gr., Phenacetin 3¾ gr., and Codeine $\frac{1}{10}$ gr.

Methylis Salicylas.—Methyl Salicylate. Methyl Ester of Salicylic Acid. $C_6H_4(OH)COOCH_3$.

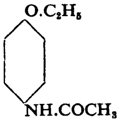
CHARACTERS.—A colourless liquid; odour characteristic, aromatic; taste sweetish, warm, aromatic. *Solubility.*—Slightly in water; miscible with fats and oils.

ACTIONS AND USES

Methyl Salicylate is readily absorbed from the skin; it irritates and later paralyses the sensory endings, and is, therefore, a valuable **rubefacient** and superficial **anodyne.** It is employed, commonly in association with Menthol, in the form of liniments and ointments (10 to 50 per cent. with Olive Oil or an ointment basis) in the local treatment of rheumatic joints, lumbago, muscular rheumatism or fibrositis and neuralgia; the absorbed ester has slight actions like Salicylates. It is used as an antiseptic and flavouring agent in tooth pastes.

Oleum Gaultheriæ, Oil of Wintergreen, which is chiefly methylsalicylate, has the same actions and uses.

Phenacetinum.—Phenacetin. Acetophenetidin. Aceto-*p*-phenetidin. $CH_3CO.NH.C_6H_4.OC_2H_5$.



CHARACTERS.—White, glistening, scaly crystals; odourless; taste slightly bitter. *Solubility.*—Very sparingly in water. Boiled with HCl and then diluted gives a violet to ruby-red colour with potassium dichromate solution.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

Preparations

1. **Tabellæ Phenacetini.**—0·3 G (5 gr.) in each.
2. **Tabellæ Acidi Acetylsalicylici et Phenacetini.**—(*See* p. 365).
3. **Tabellæ Codeinæ Compositæ.**—(*See* p. 300).

ACTIONS AND USES

Phenacetin is a **powerful antipyretic.** It produces this effect by so altering the heat-regulating mechanism in the hypothalamus as to lower the point of thermal equilibrium; as a result of this the cutaneous vessels are dilated and perspiration ensues. It quickly reduces the temperature in fever and without inducing shivering, but has little effect on the normal temperature unless given in toxic doses, and is of little use in malaria and acute rheumatism. The maximum reduction in temperature occurs in about 2 hours. Phenacetin is slowly decomposed in the body into para-amino-phenol, and this may cause methæmoglobinæmia and consequent cyanosis and breathlessness, but such poisoning or cutaneous rashes are uncommon from Phenacetin.

Phenacetin is also a **nervous sedative and anodyne.** It diminishes sensibility to pain and touch by depressing the thalamic cell station on the path of the pain fibres; thus it often gives prompt relief in nervous headache, migraine, neuralgia, neuritis, muscular rheumatism, locomotor ataxy, gout and rheumatism. By giving relief from pain it indirectly facilitates sleep but is not itself a hypnotic. Its advantage lies in the fact that it relieves pain without interfering with the functions of the cerebral cortex. For headaches and neuralgias it is often combined with Aspirin, Codeine or Caffeine.

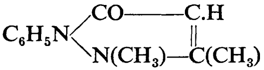
Acetanilidum (*not official*).—Acetanilide. Antifebrin. Phenyl-acetamide. $C_6H_5NH(CH_3CO)$.

CHARACTERS.—Colourless, lamellar crystals; odourless; taste slightly pungent. *Solubility*.—1 in 210 of water.
Dose.—Metric, 0·12 to 0·3 G; Imperial, 2 to 5 gr.

ACTIONS AND USES

Acetanilide is a **powerful antipyretic** by depressing the thermogenetic centre and also an **anodyne** or analgesic by depressing the thalamic cell station; hence it is used to reduce fever and to relieve pain in headache, neuralgia, sciatica and rheumatism. It is rapidly converted in the body into para-amino-phenol which causes the formation of methæmoglobin in the blood with consequent symptoms of breathlessness, cyanosis, slow and weak pulse, cold perspiration, and collapse; erythematous rashes occur commonly. If combined with Caffeine or Morphine, its toxicity is increased.

Phenazonum.—Phenazone. Antipyrin. Phenyl-dimethyl-isopyrazolone. $C_6H_5N.CO.CH.NC(CH_3)_2$.



$$C_6H_5N\begin{array}{l} \diagup CO\text{———}C.H \\ \qquad\qquad\quad\ \| \\ \diagdown N(CH_3)\text{—}C(CH_3) \end{array}$$

CHARACTERS.—Small, colourless, scaly crystals; odourless; taste bitter. *Solubility*.—1 in 1·2 of water. Aqueous solution neutral; gives deep red with Fe_2Cl_6 solution.
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

Phenazone is an **antipyretic and anodyne.** It acts like Phenacetin upon the thermogenetic centre, with consequent dilatation of the cutaneous vessels, and on the thalamic pain centres, but, being more soluble, its action is more rapidly produced and less prolonged. It is not decomposed into para-amino-phenol, and thus does not cause methæmoglobinæmia; it is excreted unchanged. It occasionally, however, causes nausea, and cutaneous rashes. Phenazone is used for the same purposes as Phenacetin.

Phenazoni Salicylas (B.P.C.).—Salipyrin. White crystals. *Solubility.*—1 in 240 of water. *Dose.*—0·3 to 1·2 G (5 to 20 gr.). It is decomposed in the duodenum into Sodium Salicylate and Antipyrin, and used like these in rheumatism and neuralgia.

Amidopyrina.—Amidopyrine. Aminopyrine. Pyramidon. Dimethyl-amino-phenyl-dimethyl-pyrazolone.$C_6H_5N.CO.C.N.(CH_3)_2.NC(CH_3)_2$.

CHARACTERS.—Colourless crystals or white powder; odourless, tasteless. *Solubility.*—1 in 18 of water; 1 in 2 of alcohol 90%.
Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

Amidopyrine acts like Phenazone, as an **antipyretic** and **anodyne**, but, being less soluble, its effects are slower and more prolonged. It is used in influenzal and infectious fevers, and for neuralgias, sciatica, etc. Idiosyncrasy to this drug is common; it inhibits the formation of granulocytes by the bone marrow and severe agranulocytosis is a common sequel of its use, which should be abandoned in favour of the safer antipyretics. Proprietary analgesics which contain it are Veramon, Allonal, Amidophen, Cibalgin, Compral, Somnosal, Trigemin, Gardan, etc. Veramon is a barbiturate of Amidopyrine with Amidopyrine; Allonal contains allyl-isopropyl barbiturate of Amidopyrine (2 gr.) with Amidopyrine (1/2 gr.).

Benzoinum.—Benzoin. Sumatra or Siam benzoin. A balsamic resin from the incised stem of Styrax Benzoin, or paralleloneurus (Sumatra Benzoin), or S. tonkinensis (Siam Benzoin). N.O. Styraceæ.

CHARACTERS.—Masses of reddish or whitish tears in a brown translucent matrix; when heated evolves fumes of benzoic acid. Odour agreeable, balsamic; taste slightly acrid.

COMPOSITION.—Benzoin contains esters of and also free *benzoic acid* and *cinnamic acid*, $C_9H_8O_2$; and two alcohols, *benzoresinol* and *coniferyl alcohol.*

Preparations

1. **Adeps Benzoinatus.**—Benzoinated Lard. Siam Benzoin, 2% in Lard.

1. **Tinctura Benzoini Composita.**—Friar's Balsam. Sumatra Benzoin, 10% with Prepared Storax, Balsam of Tolu, and Aloes, in Alcohol 90%.

Acidum Benzoicum.—Benzoic Acid. $C_6H_5.COOH$. Obtained from Benzoin, or prepared synthetically.

CHARACTERS.—Colourless, feathery crystals; odourless, taste slight. *Solubility.*—1 in 450 of water.

Sodii Benzoas.—Sodium Benzoate. $C_6H_5.COONa$.

CHARACTERS.—A white powder; no odour; taste unpleasant. *Solubility.*—1 in 2 of water.
Dose.—Metric, 0·3 to 2 G; Imperial, 5 to 30 gr.

ACTIONS AND USES

Externally.—Benzoin and its preparations are **antiseptic**; the Compound Tincture, Friar's Balsam, was formerly used as an application to small ulcers and wounds. Siam Benzoin prevents lard from becoming rancid.

Internally.—Benzoin and Benzoic Acid are slightly irritant to mucous membranes. The inhalation of the vapour from hot water, containing in a pint 60 min. of the Compound Tincture, stimulates mucous secretions and has a slight antiseptic effect in laryngitis and bronchitis.

Benzoic Acid (5 to 15 gr.) is occasionally used as a reflex expectorant in chronic bronchitis and is contained in Tinctura Opii Camphorata. Sodium Benzoate, which is less irritant to the stomach, is also a reflex expectorant. Benzoates have a weak antipyretic action which is not useful therapeutically.

Benzoic Acid and Benzoates are converted into hippuric acid by combination with glycine; they were used formerly as diuretics and urinary antiseptics. Since amino-acetic acid (glycine) is formed in the liver, the conversion of Sodium Benzoate into hippuric acid is used as a test of liver function; Sodium Benzoate, 5·9 G in 30 Mils of water, is given orally, the urine should then contain from 3 to 3·5 G of hippuric acid within four hours.

DIURETICS

Diuretics are drugs which increase the volume of the urine; there may be only greater filtration of water but usually the total solids are also excreted in larger quantities.

Diuretics may act: (1) By improving the efficiency of the circulation, and dilating or increasing the blood-flow through the renal vessels, thus bringing more glomeruli into use (*cardio-vascular diuretics*), e.g. Alcohol, Digitalis, Strophanthus, Squill, Caffeine, Theobromine, and Theophylline; (2) By increasing the hydræmia of the blood, that is, lowering its protein osmotic tension, e.g. Water, Saline Injections and Alkali Salines; the last, by raising the saline osmotic tension, draw fluid out of the tissues; (3) By reducing reabsorption of water in the tubules; this may result from (*a*) no-threshold substances, e.g. Potassium salts, and low-threshold compounds, e.g. Urea, or (*b*) potential irritants of the tubular epithelium which decrease its reabsorptive powers, e.g. volatile oils, Mercury salts; (4) By causing acidosis, e.g. Ammonium or Calcium Chloride and Ammonium Nitrate. Many of these diuretics have already been discussed.

Theobromina et Sodii Salicylas.—Theobromine and Sodium Salicylate. Diuretin. Theobromine is 3 : 7-dimethylxanthine, $C_7H_8O_2N_4$.

CHARACTERS.—A white, amorphous powder. No odour; taste sweetish, alkaline. *Solubility.*—1 in 1 of water, alkaline. Acidified with acetic acid gives violet colour with Fe_2Cl_6. Contains not less than 46% of Theobromine and 41% of Sodium Salicylate.
Dose.—Metric, 0·6 to 1·2 G; Imperial, 10 to 20 gr.

ACTIONS AND USES

Theobromine acts like Caffeine (p. 262) and other xanthine derivatives as a **diuretic**, but it does not stimulate the cerebrum or medulla. It acts as a diuretic by dilating the renal vessels and by accelerating the heart, thus increasing the blood-flow through the kidney so that more glomeruli are brought into action, glomerular filtration is increased and time for tubular reabsorption diminished. Theobromine acts more rapidly and powerfully as a diuretic than Caffeine and does not make the patient wakeful.

Theobromine and Sodium Salicylate is largely used in the treatment of œdema in cardiac disease, and when given with Digitalis the diuretic effect is increased and more prolonged. In nephritis its effects are uncertain; generally the response is better in chronic interstitial than in chronic parenchymatous nephritis, but it may increase the excretion of albumin and Potassium Citrate is preferable.

Theobromine, by its peripheral vaso-dilator effect, lowers blood-pressure; it has proved of value in the treatment of hyperpiesia, and, as it dilates the coronary vessels, in angina pectoris; it may be prescribed in these cases with Phenobarbitone as a sedative.

Theophyllina.—Theophylline. 1 : 3-dimethylxanthine. $C_7H_8O_2N_4,H_2O$. An alkaloid from the leaves of Camellia sinensis or made synthetically

CHARACTERS.—A white, crystalline powder; taste bitter. *Solubility.*—1 in 120 of water.

Dose.—Metric, 60 to 200 mg; Imperial, 1 to 3 gr.

Theophyllina cum Æthylenediamina.—Theophylline with Ethylenediamine. Aminophylline, Euphylline. Contains about 75% of Theophylline and 12% of Ethylenediamine, $C_2H_8N_2$.

CHARACTERS.—White or yellowish granules, taste bitter; *Solubility.*—1 in 5 of water.

Dose.—Metric, 0·1 to 0·5 G; Imperial, 1½ to 8 gr.

Preparation

Injectio Theophyllinæ cum Æthylenediamina.—A sterile solution in Water for Injection, free from CO_2.

For intravenous injection: **0·25 G (4 gr.) in 10 Mils (150 min.)**
For intramuscular injection: **0·5 G (8 gr.) in 2 Mils (30 min.).**

Theophyllina et Sodii Acetas.—Theophylline and Sodium Acetate. Theocine. Contains 55% Theophylline.

CHARACTERS.—A white, crystalline powder; odourless; taste bitter. *Solubility.*—1 in 25 of water (alkaline).

Dose.—Metric, 0·12 to 0·3 G; Imperial, 2 to 5 gr.

ACTIONS AND USES

Theophylline, which has a slight cerebral stimulant action, is a more powerful diuretic than Caffeine or Theobromine. Theophylline Sodium Acetate or Theophylline Ethylenediamine is given orally as a diuretic during the first few days of Digitalis treatment for cardiac œdema; the former preparation is more likely to cause nausea. Theophylline is contained in Injectio Mersalyli to prevent its decomposition and hasten its excretion. In renal œdema, Theophylline is not advised as it may increase the albuminuria and give rise to renal irritation.

Theophylline lowers blood-pressure and dilates the coronary vessels better than Theobromine; Theophylline Ethylenediamine is used in hypertension and angina; the Ethylenediamine is believed to aid the dilator effect as well as increase the solubility of Theophylline.

Theophylline dilates the bronchioles and has some protective effect against histamine spasm. Theophylline Ethylenediamine is, therefore, frequently prescribed for asthmatic attacks, or as a preventive of their recurrence, and also for emphysema. It is valuable in cases of status asthmaticus which have not responded to Adrenaline; it may then be given either by very slow intravenous injection, or in less acute cases by intramuscular injection in the strengths stated.

Theophylline Monoethanolamine (Theamin) is also used in asthmatic attacks either orally, 1½ to 3 gr. in capsules, or by intravenous or intramuscular injection in similar strengths and doses to those of Theophylline Ethylenediamine.

Urea.—Carbamide. Diamide of carbonic acid. $CO(NH_2)_2$.

CHARACTERS.—Colourless, prismatic crystals; almost odourless; taste cool, saline. *Solubility.*—1 in 1 of water.

Dose.—Metric, 5 to 15 G; Imperial, 75 to 225 gr.

ACTIONS AND USES

Urea is a useful **diuretic**, because as it is only slightly reabsorbed by the tubules (low-threshold substance), it prevents the normal reabsorption of water by raising the osmotic tension of the urine. Liquor Ammonii Acetatis, being excreted as Urea, acts in the same way. The *Urea Concentration Test* is valuable for estimating renal efficiency: 15 G (230 gr.) Urea are given by mouth in 100 c.c. water; the Urea in the urine is estimated after one and two hours; if the percentage is 2 per cent. or more, renal function is efficient.

URINARY ANTISEPTICS

These inhibit the growth of organisms in the urinary tract. They act—(1) By making the urine acid or more acid: Ammonium Chloride, Ammonium Nitrate, Calcium Chloride, Acid Sodium Phosphate, Boric, Benzoic and Salicylic Acids. (2) By making the urine alkaline; Potassium Acetate or Citrate, Sodium Citrate, Potassium or Sodium Bicarbonates. (3) By excretion in the urine as antiseptic or bacteriostatic agents; Sulphonamides (*see* p. 399), Penicillin (*see* p. 412), Hexamine as Formaldehyde and Ammonium Mandelate as Mandelic Acid. Sulphonamides and Penicillin have largely displaced other urinary antiseptics.

Hexamina (B.P.C.).—Hexamine. Hexamethylene-tetramine. Urotropine. Methenamine. $(CH_2)_6N_4$. Colourless crystalline powder. Inodorous; taste sweetish, then bitter. *Solubility.*—1 in 1·5 of water.

Dose.—Metric, 0·6 to 2 G; Imperial, 10 to 30 gr.

ACTIONS AND USES

Hexamine is hydrolyzed by acids into formaldehyde and ammonia. When given orally it is rapidly excreted by the kidney and, if the urine be acid, the formaldehyde liberated has a slight antiseptic action. Urinary acidity is ensured by giving Acid Sodium Phosphate or Ammonium Chloride an hour before the

Hexamine. It has been supplanted by the Sulphonamides and Penicillin, which are much more effective in urinary infections. Hexamine was also given for cholecystitis, but it had no antiseptic action as the bile is alkaline.

Hexyl-Resorcinol. Caprokol. $C_6H_3(OH)_2(CH_2)_5CH_3$. *Dose.*—0·12 to 0·6 G (2 to 10 gr.) in 25% solution in Olive Oil thrice daily after meals; given in gelatin capsules.

ACTIONS AND USES

Hexyl-Resorcinol is a **urinary antiseptic** acting equally well in acid or alkaline urines. By lowering the surface tension of the urine it readily diffuses into the renal tissues and bacteria. It is sometimes useful in the treatment of pyelitis and cystitis due to Gram-positive organisms.

Hexyl-Resorcinol is also **anthelmintic** for round-, thread-, hook- and small tapeworms, the dosage being 1 G (15 gr.) or, for children under six, 0·6 G (10 gr.) and, over six, 0·8 G (12 gr.) dissolved in Olive Oil and taken in a capsule. One dose, followed in two hours by a purgative, may suffice to remove roundworms. Three doses at intervals of three days are given for hookworms and for threadworms, the latter being treated locally also by retention enemas of 0·1 per cent. Hexyl-Resorcinol in Water.

Pyridium.—Phenyl-azo-diamino-pyridine hydrochloride. A red crystalline powder. *Dose.*—0·1 to 0·2 G (1½ to 3 gr.) as tablets before meals. It is excreted in the urine where it has an antiseptic action. It may cause headache, nausea, and colic, and should be avoided in nephritis and hepatitis.

Acidum Mandelicum.—Mandelic Acid. Phenylglycollic Acid. $C_6H_5.CHOH.COOH$.

CHARACTERS.—White crystals turning yellow in light; taste, and saline. *Solubility.*—1 in 7 of water.
Dose.—Metric, 2 to 4 G., Imperial, 30 to 60 gr. (Neutralized by Ammonium Hydroxide or Sodium Bicarbonate).

Calcii Mandelas.—Calcium Mandelate.

CHARACTERS.—A white powder, taste saline; very slightly soluble in water.
Dose.—Metric, 2 to 4 G; Imperial, 30 to 60 gr.

ACTIONS AND USES

A high fatty or ketogenic diet, which results in the excretion of β-hydroxybutyric acid, has a powerful inhibitory action on the growth of organisms in the excretory organs; but few patients will tolerate a fatty dietary for long. Mandelic Acid, the least toxic of the hydroxy acids, was found to be equally efficient as a bacteriostatic agent, provided the urine was maintained at an acidity of *p*H 5·3, and it may be necessary to reduce the fluid intake. When Mandelic Acid, neutralized by Sodium Bicarbonate, or Sodium Mandelate, is given, it is essential that Ammonium Chloride in 1 G (15 gr.) doses—in cachets to conceal its taste—should also be given four times daily in order to lower the *p*H of the urine to the requisite acidity. If Ammonium Mandelate is administered, the Ammonium ion is converted to urea and the Mandelic Acid thus liberated acidifies the urine and so enables the dosage of Ammonium Chloride to be reduced or omitted. Sodium or Ammonium Mandelate is prescribed along with flavours such as Liquid Extract of Liquorice, and Syrup of Lemon or Orange, in ½ fl. oz. of Chloroform Water, after meals.

Calcium Mandelate is given as a powder, suspended in some flavoured water. It has the advantages that, being less soluble, it has a less unpleasant taste, is less irritating to the stomach and itself; on liberating Mandelic Acid, gives rise to an acid urine, thus less or no Ammonium Chloride need by given. Mandecal contains 75 per cent. of Calcium Mandelate.

Mandelic Acid therapy has proved of curative value in acute and chronic pyelitis, pyelonephritis, cystitis and bacilluria, and is often successful in cases which fail to respond to Sulphonamides or Penicillin. It is most effective against infections by E. coli, but cases of infection with Streptococcus fæcalis, and Staphylococcus albus, but rarely B. proteus, have also been cured. Infections in children, who are given 10 to 20 gr. according to age, are generally cured by this treatment. Mandelic Acid therapy occasionally causes diarrhœa, and contra-indications to its use are urinary obstruction, renal insufficiency and acute febrile cases, as it may cause irritation and albuminuria.

Urinary antiseptics formerly used were Buchu, Copaiba, Oleum Cubebæ and Oleum Santali. They owed their antiseptic action to the excretion of their volatile oils by the kidney; they acted also as diuretics by moderate irritation but were liable to cause albuminuria.

DRUGS INFLUENCING GOUT

Colchicum has an obscure action in acute gout. Cinchophen lowers the renal threshold for uric acid and thus aids its removal.

Colchici Cormus.—Colchicum Corm. The sliced and dried corm of Colchicum autumnale, Meadow Saffron. N.O. Liliaceæ.

CHARACTERS.—Dry, reniform, thin slices; firm, white starchy; taste bitter.

COMPOSITION.—Dried Corm contains 0·4% of the alkaloid, *colchicine*, $C_{22}H_{25}NO_6$, tannic acid, starch, sugar, gum, etc.

Preparation

Extractum Colchici Siccum.—A dry extract made with Alcohol 60% and added Lactose. Contains 1% of Colchicine.
Dose.—Metric, 10 to 30 mg; Imperial, 1/6 to 1/2 gr.

Colchici Semen.—Colchicum Seed. The dried, ripe seeds of Colchicum autumnale.

CHARACTERS.—Small, ovoid, reddish-brown, pitted seeds, pointed at the hilum. Taste bitter, acrid.

Preparations

1. **Extractum Colchici Liquidum.**—A liquid extract made with Alcohol 60%. Contains 0·3% of Colchicine.
Dose—(*Not official*). **Metric, 0·12 to 0·3 Mil; Imperial, 2 to 5 min.**
2. **Tinctura Colchici.**—Liquid Extract 10% in Alcohol. Contains 0·03% of Colchicine.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.

Colchicina.—Colchicine, an alkaloid from the corm and seeds of Colchicum autumnale. $C_{22}H_{25}NO_6$.

CHARACTERS.—Pale-yellow crystals, scales or powder darkening in light, taste bitter; readily soluble in water and alcohol.
Dose.—*Orally:* **Metric, 0·5 to 1 mg; Imperial, 1/120 to 1/60 gr.**
Total dose: **Metric, 2 to 8 mg; Imperial, 1/30 to 1/8 gr.**

ACTIONS AND USES

Internally.—Colchicum in moderate dose causes, after a delay of one to three hours, vomiting, increased intestinal secretion and peristalsis resulting in diarrhœa due to capillary vaso-dilatation produced by Colchicine in the gastro-intestinal tract. After a preliminary decrease, Colchicum greatly augments the number of polymorphonuclears in the blood. Toxic doses after 3 to 6 hours induce a motor and sensory paralysis which travels from below upwards till the respiratory nerves are involved and death results; the slow onset of these effects may be due to the formation of the more toxic oxydicolchicine.

As a **specific for acute gout**, Colchicum relieves the pain and inflammation, and shortens the duration of attacks in young and robust subjects to about a day. It is usually given as the Tincture in full dose at four-hourly intervals until relief is obtained. Potassium Bicarbonate may be given at the same time to lower the urinary acidity.

Colchicine is regarded as more reliable in its effects; a dose of

1 mg (1/60 gr.) is given at first and then 0·5 Mg (1/120 gr.) doses at two-hourly intervals till pain is relieved or vomiting or diarrhœa commences. Colchicum is of less value in the chronic gout of elderly subjects; and is useless in rheumatoid arthritis. The unquestionable influence of Colchicum in acute gout is unexplained, as is the pathology of this disease. Colchicum does not produce any constant effect on the excretion of uric acid, as was once supposed.

Cinchophenum.—Cinchophen. Phenyl-cinchoninic Acid. Quinophan. Phenyl-quinoline carboxylic acid. $C_6H_5.C_9H_5N.COOH$.

CHARACTERS.—White or yellowish powder or crystals; almost odourless; taste slightly bitter. *Solubility.*—Insoluble in water, soluble in alkalis.

Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.

ACTIONS AND USES

Cinchophen is a valuable **remedy in chronic gout**; it **increases the excretion of uric acid** by lowering its renal threshold; the increased excretion reaches a maximum in about three hours and then declines, but repeated dosage maintains for about two days a high rate of elimination; in consequence the uric-acid content of the blood is lowered and the liability to recurrence of attacks is diminished. There is also increased excretion of urates and urea. It is prescribed in tablets containing 5 or 8 gr. thrice daily for three days only at a time, and each dose followed by a large draught of water containing 60 gr. of Sodium Bicarbonate to aid solution of the uric acid.

Cinchophen is an antipyretic and analgesic by an action on the basal ganglia. In acute gout, it is not so effective as Colchicine but it usually mitigates the pain. It is too risky for use as an antipyretic or as an anodyne in chronic rheumatic conditions.

Toxic Effects.—Cinchophen must be given with great care, as excessive doses or continued use may cause digestive disturbances, skin rashes, jaundice and necrosis of the liver (acute yellow atrophy). Patients vary widely in susceptibility, therefore it is advisable to use it only during two or three successive days in any week and to stop it if appetite becomes impaired; a diet rich in glucose lessens the risk of liver damage.

Neocinchophenum (U.S.P.).—Ethyl-methyl ester of Cinchophen. *Dose.—0·3 to 1 G (5 to 15 gr.) three or four times daily for four days is also used in acute and chronic gout along with Sodium Bicarbonate.*

UTERINE STIMULANTS

Ecbolics stimulate uterine contractions and **abortifacients** cause death or expulsion of the fœtus from the pregnant uterus. **Emmenagogues** increase the menstrual flow.

Drugs which increase uterine contractions or tone may act (*a*) by direct stimulation of the uterine muscle, e.g. Ergometrine, Oxytocin (Posterior Pituitary), Quinine and Histamine; (*b*) by stimulating the motor sympathetic endings, e.g. Ergotoxine, Ergotamine (small doses) and, in human, rabbit and pregnant cat uteri, Adrenaline. Indirectly, by irritation of the colon and causing pelvic congestion, Aloe and drastic purgatives may excite contractions, and, by irritating the urinary tract, volatile oils such as Turpentine, Savin, Rue and Pennyroyal have been credited with causing uterine contractions and possibly abortion.

Ergota.—Ergot. Secale Cornutum. The sclerotium (resting stage) of the fungus Claviceps purpurea, N.O. Pyreno-mycetes, occurring in the ovary of Secale cereale, the Rye. Ergot should be thorougly dried and kept entire in air-tight containers. It contains, calculated as ergotoxine, 0·2% total alkaloids of which not less than 15%, calculated as ergometrine, are water soluble.

CHARACTERS.—Small, dark violet-brown, cylindrical, curved and tapering pieces; longitudinally furrowed and cracked; pinkish-white within. Odour peculiar; taste disagreeable.

COMPOSITION.—Ergot contains the active principles: (1) six isomeric pairs of alkaloids which are derivatives of lysergic acid and vary in amounts in samples of Ergot from different countries; the lævorotatory member of each pair has the pharmacological action, the isomer being practically inert. The most important alkaloids are *ergometrine*, which is water-soluble and stimulates uterine muscle directly; *ergotamine* and *ergotoxine*, which latter is now known to consist of a variable mixture of three alkaloids, ergocornine, ergocrystine and ergokryptine. (2) Various amines, e.g. *tyramine*, *p*-hydroxyphenyl-ethylamine, $OH.C_6H_4.CH_2CH_2NH_2$, having an action like Adrenaline, and *histamine*, β-iminazolyl-ethylamine, $C_5H_9N_3$, which lowers blood-pressure but contracts plain muscle and possesses ecbolic action. There is also 40% of fixed oil and some *acetyl-choline*.

Ergota Præparata.—Prepared Ergot. Ergot powdered and immediately deprived of fat by percolation with light petroleum and dried. Contains 0·2%, calculated as Ergotoxine, of total alkaloids of which not less than 15%, calculated as Ergometrine are water soluble. 0·5 G (8 gr.) contains 1 mg (1/60 gr.) of total alkaloids and 0·15 mg (1/400 gr.) of water-soluble (ergometrine) alkaloids.

Dose.—Metric, 0·15 to 0·5 G; Imperial, 2½ to 8 gr.

Preparations

1. **Tabellæ Ergotæ Præparatæ.**—0·15 G (2½ gr.) in each.
2. **Extractum Ergotæ Liquidum.**—Liquid Extract of Ergot. Ergot is first defatted by percolation with light petroleum and then percolated with 50% alcohol containing 1% tartaric acid. The extract contains 0·04% total alkaloids, calculated as Ergotoxine. 1·2 Mils (20 min.) contains 0·7 mg (1/90 gr.) alkaloids.
Dose.—Metric, 0·6 to 1·2 Mils; Imperial, 10 to 20 min.

Ergometrinæ Maleas.—Ergometrine or Ergonovine Maleate. Ergobasine. $C_{19}H_{23}O_2N_3,C_4H_4O_4$. The acid maleate of Ergometrine.

CHARACTERS.—A white or yellowish powder. *Solubility.*—1 in 36 of water, with blue fluorescence.

Dose.—*Orally:*
Metric, 0·5 to 1 mg; Imperial, 1/120 to 1/60 gr.
By intramuscular injection:
Metric, 0·25 to 0·5 mg; Imperial, 1/240 to 1/120 gr.
By intravenous injection:
Metric, 0·125 to 0·25 mg; Imperial, 1/480 to 1/240 gr.

Preparation

Injectio Ergometrinæ Maleatis.—A sterile solution in Water for Injection, containing 0·5 mg (1/120 gr.) in 1 Mil (15 min.).

Ergotaminæ Tartras.—Ergotamine Tartrate. $(C_{33}H_{35}O_5N_5)_2,C_4H_6O_6$.

CHARACTERS.—Colourless crystals or a white powder; readily soluble in water, but becomes turbid.

Dose.—*Orally, single:*
Metric, 1 to 2 mg; Imperial, 1/60 to 1/30 gr.
By subcutaneous injection:
Metric, 0·25 to 0·5 mg; Imperial, 1/240 to 1/120 gr.

ACTIONS AND USES

Ergometrine is the most valuable alkaloid in Ergot. It differs from Ergotamine and Ergotoxine thus: (1) it **contracts the uterus** by direct stimulation of its muscle; (2) its action in stimulating uterine contractions and tone is produced more rapidly, thus Ergometrine, given orally, acts **within 6 to 8 minutes** or, given intramuscularly, within 3 to 5 minutes, or given intravenously within one minute (Ergotoxine takes 20 or 30 minutes to act); (3) the action of Ergometrine is less prolonged, lasting 3 or 4 hours (Ergotoxine, 6 or more hours); (4) it has about 1/4 the general toxicity of Ergotoxine and rarely causes headache, nausea, and nervous depression; (5) its power of constricting blood-vessels is much less than that of Ergotoxine, therefore, it rarely causes gangrene.

Ergotoxine and Ergotamine, in small doses, stimulate the receptors for the cells controlled by the motor sympathetic nerve endings. If Ergotoxine be injected, it produces at first **a large and prolonged increase in blood-pressure** by constricting the arterioles, mainly in the splanchnic area, but also in the limbs.

Large doses of Ergotoxine paralyse the motor sympathetic receptors with the result that if Adrenaline be now given or the sympathetics be stimulated, a fall—instead of the usual rise—of blood-pressure will occur because the vaso-dilator receptors only will be stimulated. The intense vascular constriction produced by Ergotoxine is the cause of gangrenous ergotism.

Ergotamine and ergotoxine also powerfully **increase the rhythmic contractions and tone of the uterus** and produce a prolonged muscular spasm of this organ, but they do not influence the bronchioles. The heart is affected reflexly by the rise in pressure and is slowed.

Ergotoxine is absorbed from the intestine, but when given by mouth its action is uncertain and it takes about half an hour to an hour to influence the uterus. Even if injected there is a latent period of 20 to 30 minutes before the uterus is stimulated, but the tonic contraction lasts for six or more hours.

Actions and Uses of Ergot.—When Prepared Ergot or Extractum Ergotæ Liquidum is given by mouth its action is essentially that of Ergometrine, and the action on the uterus begins within ten minutes. In human subjects only a slight rise in blood-pressure results from the vaso-constriction. The **uterus,** particularly during parturition, responds by **increase in the force and frequency of its rhythmic contractions and by a marked increase in tone,** which is commonly maintained for one or two hours.

Ergot is used **in labour** either as Ergometrine Maleate, Ergota Præparata, or as Extractum Ergotæ Liquidum by mouth during the third stage of labour. **When the uterus is empty, it is very valuable** to expel clots and ensure contraction of the womb, whilst in **post-partum hæmorrhage** it is invaluable in exciting and maintaining a powerful tonic contraction of the uterus; in urgent cases, Ergometrine is given intravenously. The use of Ergot before the second stage is well advanced may be dangerous as it contracts the os uteri and may cause harmful pressure on the child or rupture of the uterus. Ergot is also employed with considerable success in the treatment of uterine hæmorrhage arising from polypus uteri, chronic metritis, fibroid tumours, myoma, and in menorrhagia, but large prolonged dosage has led to gangrene of the toes.

Ergometrine Maleate in dose of 1 mg (1/60 gr.) by mouth, 0·5 mg (1/120 gr.) intramuscularly, or 0·125 mg (1/480 gr.) intravenously, is a prompt means of ensuring a tonic contraction of the uterus in post-partum hæmorrhage, in the uterine inertia which may follow Cæsarean section, and in the treatment of uterine hæmorrhage associated with tumours or the menopause. If an initial dose is given intramuscularly, the uterine contraction can be maintained by oral dosage after three hours.

Ergotamine Tartrate.—*Dose.*—0·25 mg (1/240 gr.) in 0·5 Mil, by subcutaneous injection, is remarkably effective for unknown reasons in relieving migraine and recurrent headaches within thirty minutes to two hours; possibly it may constrict the cerebral vessels. Oral administration of 2 mg (1/30 gr.) produces similar relief within two to three hours but a more rapid response and from smaller dosage is obtained from sublingual absorption. Larger doses may be necessary in severe cases, but they are apt to cause nausea and vomiting, muscular pains and weakness, and tingling in the fingers and toes. Ergotamine does not cure the disease, and dosage must be spaced with care because of the danger of inducing gangrene.

Ergotism.—From the prolonged use of ergotized rye as an article of diet, chronic poisoning has occurred in epidemics on the Continent; these were most common in the early autumn when the Ergot was in active condition. There are two forms: (1) **Gangrenous Ergotism**, due to constriction and closure of the peripheral vessels by Ergotoxine; the distal pulse is hard and small, peripheral parts—fingers and toes or the ear—become pale and cold and an exfoliative dermatitis or typical dry gangrene develops. (2) **Nervous Type** : Usually patients complain first of formication, as if insects were on the skin; headache and drowsiness with other sensory disturbances follow and, in later stages, painful twitchings and cramps of the limb muscles, inco-ordinate gait, intermittent flexor contractures of the limbs or clonic convulsions may occur. This type may be due not only to Ergot but also to subacute combined degeneration of the spinal cord from lack of Vitamine A in famine conditions.

HISTAMINE AND ANTI-HISTAMINIC DRUGS—DIMERCAPROL (B.A.L.)

Histaminæ Phosphas Acidus.—Histamine Acid Phosphate. The di-acid phosphate of 4-β-aminoethylglyoxaline. $C_2H_3N_2.CH_2.CH_2NH_2,2H_3PO_4$.

CHARACTERS.—Colourless crystals; soluble 1 in 4·5 of water.

Dose.—*By subcutaneous injection:*

Metric, 0·5 to 1 mg; Imperial, 1/120 to 1/60 gr.

Preparation

Injectio Histaminæ Phosphatis Acidi.—A sterile solution in Water for Injection, containing 1 mg (1/60 gr.) Histamine Acid Phosphate in 1 Mil (15 min.) for subcutaneous injection.

ACTIONS AND USES

Intradermally.—If a drop of 1 : 1,000 solution of Histamine Acid Phosphate is applied to the skin and a puncture or scratch (intradermal injection) is made below it, a "triple response" occurs, comparable with that which follows heavy stroking, namely after a brief latent period there appears a sharply defined red line or spot due to capillary dilatation; then 30 seconds later, a diffuse flare with irregular margins develops owing to dilatation by an axon reflex of the local arterioles; and, finally, in about 2½ minutes, a white wheal raised above the epidermal surface is indicative of the increased permeability of the capillaries and the escape of plasma into the local tissues. This reaction is delayed in Raynaud's disease and in advanced arterio-sclerosis.

Subcutaneously.—If Histamine is injected, it stimulates the smooth muscles of the body, causing contraction of the bronchial, intestinal and uterine muscles, but, in man, it dilates the arterioles as well as the capillaries and increases the capillary permeability. An injection of Histamine produces, therefore, a **large and prolonged fall in blood-pressure** with symptoms resembling surgical shock, anaphylaxis, or allergy, and, owing to the reduced blood-pressure, the blood supply and functions of the vital organs are impaired.

The absorption of Histamine or a related amine (H-substance) derived from damaged tissues is a factor in the production of surgical shock. In allergy and anaphylactic shock, liberation of Histamine appears to take place from sensitized tissues, and gives rise to the urticarial rashes or erythemas, flushing, œdema and itching of the skin, dyspnœic or asthmatic attacks and reduced blood-pressure, which are symptomatic of allergy. Some drug idiosyncrasies, e.g. from Salicylates, Quinine, Thiouracil, Sulphonamides, Penicillin and Organic Arsenicals, are of allergic character, and apparently originate from Histamine liberated from sensitive or sensitized tissues. Against such allergic reactions, anti-histaminic drugs have proved useful.

Histamine Acid Phosphate is given by subcutaneous injection, because, if given orally, it is destroyed in the alimentary tract.

Histamine Acid Phosphate produces an increased secretion of hydrochloric acid and water from the gastric glands without influencing the pepsin secretion. If, after giving a test meal, 1/2 to 1 Mil (7 to 15 min.) of a 1: 1,000 solution is injected hypodermically and no acid is found between 20 and 40 minutes afterwards in the stomach contents, achlorhydria is established. Such injections are sometimes necessary to distinguish achylia gastrica of pernicious anæmia from chronic gastritis and carcinoma.

Mepyramine Maleate.—Anthisan. Neoantergan Maleate. Pyranisamine Maleate. N-dimethylaminoethyl-(N-*p*-methyoxybenzyl)-*α*-aminopyridine maleate.

Dose.—*Orally* in tablets:

Metric, 50 to 100 mg; Imperial, 3/4 to 1½ gr. to a daily maximum of 1 G (15 gr.).

By injection:

1 to 2 Mils of a 2·5% solution to a maximum of 0·2 G (3 gr.) daily.

Diphenhydramine.—Benadryl. *β*-dimethylaminoethyl-benzhydryl-ether hydrochloride.

Dose.—*Orally* in capsules:

Metric, 25 to 100 mg; Imperial, 2/5 to 1½ gr.

By injection:

10 to 50 mg (1/6 to 3/4 gr.) in Normal Saline.

Antazoline.—Antistin. 2-(N-phenyl-N-benzylamino)-methylimidazoline.

Dose.—*Orally* in tablets:

Metric, 100 to 200 mg; Imperial, 1½ to 3 gr.

By injection:

100 mg. (1½ gr.) in 2 mils.

Tripellenamide.—Pyribenzamine. N′-pyridyl-N′-benzyl-N-dimethylethylenediamine hydrochloride.

Dose.—*Orally:*

Metric, 50 to 100 mg; Imperial, 3/4 to 1½ gr.

ACTIONS AND USES

These anti-histaminic drugs are derived from dimethylethylenediamine or from the benzhydryl ether of *β*-dimethylaminoethanol. Their anti-histaminic action appears to be a protective one upon the tissue cells because relapses are liable to occur on stopping or reducing dosage. They counteract the vaso-dilator actions of Histamine, relieve the itching, reduce capillary permeability, and prevent the development of Histamine wheals. They also relax spasm in smooth muscle produced by Histamine and by Acetylcholine; they do not inhibit the action of Histamine on the acid secretion of the stomach.

These drugs are usually given orally in capsules, tablets or elixirs three or four times daily, but in acute cases, subcutaneous, intramuscular, or well-diluted intravenous administration may be used. Creams (2 per cent.) are available for the local treatment of allergic œdemas and pruritus.

The drugs give symptomatic relief from itching pain, catarrhs or bronchial spasm in sensitization dermatitis, acute and chronic urticarias, pruritus, vaso-motor rhinitis, hay fever and allergic serum and drug reactions, e.g. from Penicillin, Liver Extracts and Insulin. They are commonly successful in angio-neurotic œdema but are less reliable in giving relief from allergic asthma.

Side-effects arising from these drugs include drowsiness, headache, dizziness, nervousness, dry mouth, nausea, muscular pains and numbness of the extremities, and these may necessitate reduction in dosage.

Promethazine.—Phenergan. N-(2-dimethylamino-*n*-propyl) phenthiazine hydrochloride. Available in 25 mg. tablets. This is a slowly acting but prolonged, powerful, anti-histaminic drug, used in allergic conditions; but it may cause mental confusion and sleep, hence it is usually given in the evening.

Dimercaprol (B.P.C.).—British Antilewisite. B.A.L. 2 : 3-dimercaptopropanol. $CH_2(SH).CH(SH).CH_2OH$.

CHARACTERS.—A colourless, mobile liquid, with alliaceous odour. *Solubility.*—1 in 16 of water; mixes with Benzyl Benzoate and the mixture may be diluted with Arachis Oil.

Dose.—(*Not official*).

1·5 to 3 mg per Kg (1/90 to 1/45 gr. per lb.) body weight.

ACTIONS AND USES

Dimercaprol is an **antidote to poisoning by heavy metals**, such as Mercury, Gold, Arsenic and Bismuth. It was originally evolved as an antidote to the arsenical vesicant gases. The toxic action of these heavy metals seems to arise from impairment of the tissue pyruvate-oxydase system by their affinity for sulphydryl (–SH) groups; this dithiol compound combines more readily than the dithiol protein groups with these metals to form compounds which are excreted by the kidneys.

Dimercaprol is given by deep intramuscular injection into the thigh or buttock of a 5 per cent. solution in Arachis Oil, containing 10 to 20 per cent. of Benzyl Benzoate as a solvent. Initially, 4 doses of 2 Mils (30 mins.) are given at 4-hourly intervals; on the next 3 days, 2 doses per day; and then 1 dose per day for 2 or more days. Doses above 3 to 5 mg per Kg body weight give rise to lachrymation, salivation, burning sensations in the mouth, throat and eyes, vomiting and rise of blood-pressure, but these usually last for only a few hours.

Dimercaprol has proved successful as an antidote in the toxic complications from the injection of heavy metals, namely for jaundice, agranulocytosis, optic neuritis and encephalitis, but not for aplastic anæmia. Most cases of arsenical exfoliative dermatitis are greatly improved within 3 weeks and dermatitis from gold injections usually disappears rapidly. Mercurial poisoning is more resistant to Dimercaprol.

EXTERNAL PROTECTIVES AND EMOLLIENTS

Protectives are drugs which form a superficial covering over the skin, protect it from contact with cold and dry air, strong sunlight, or micro-organisms, and check the evaporation of water from the epithelial cells. **Emollients** are drugs which soften the superficial layers of the skin and render the skin pliable. Such drugs are either insoluble dusting powders, e.g. Creta, Magnesium Silicate (French Chalk), Zinc Oxide, etc., or oils and fats.

Oleum Olivæ.—Olive Oil. The oil expressed from the ripe fruit of Olea europæa, N.O. Oleaceæ.

CHARACTERS.—Pale or greenish-yellow; odour faint; taste bland; below 10° C. becomes pasty.

COMPOSITION.—Olive Oil consists of 72% of fluid oils, *olein*, $C_3H_5(C_{17}H_{33}COO)_3$, and *linolein*; and 28% of solid oils *palmitin* $C_3H_5(C_{15}H_{31}COO)_3$, and *arachin*. These are compounds of the radical *glyceryl*, C_3H_5, with *oleic acid*, $C_{17}H_{33}COOH$, and *palmitic acid*, $C_{15}H_{31}COOH$, respectively.

ACTIONS AND USES

Externally applied, Olive Oil is **emollient**; it renders the skin smoother, softer and more flexible. It is used to facilitate massage and, in liniments, to aid the penetration of rubefacients such as Camphor into the skin. It is an emergency **protective** after burns, corrosive acids and alkalis, by coating the surface and excluding air. Olive Oil, if massaged into the skin, is absorbed by the lymphatics; this treatment has a **nutritive** value in wasted children.

Internally, Oils may be given as **demulcents** in corrosive poisoning, except by Phosphorus. In the stomach, fixed oils in 1/2 oz. doses before meals materially reduce the secretion of hydrochloric acid from the stomach and are therefore valuable, especially in the form of milk and cream, in **hyperchlorhydria**. In the duodenum they are emulsified and split up by the pancreatic lipase in the alkaline fluid into glycerol and fatty acids, which combine with alkalis to form soaps. In many persons oils cause nausea and dyspepsia; they may also have a slight laxative action by lubricating the upper intestine before they are absorbed. Olive Oil may be used as a laxative enema, but soap enemas are better.

The Oil is resynthesized from its products in the intestinal epithelium; it enters the blood through the lacteals and lymphatics. In the body it is either fully oxidized into carbonic acid and water and constitutes a **food**, or increases the amount of fat in the tissues. Defective metabolism of fats by the liver leads to the presence of β-hydroxybutyric acid, aceto-acetic acid and acetone in the blood, a condition which may arise in diabetes and in Chloroform and Phosphorus poisoning.

Olive or other vegetable oils do not contain Vitamins A or D. Olive Oil is used as a salad oil and may be taken by some patients in the form of Sardine Oil when other fats are refused.

Oleum Arachis.—Arachis Oil. Earth-nut, Ground-nut, or Pea-nut Oil. The oil expressed from the seeds of Arachis hypogæa, N.O. Leguminosæ.

CHARACTERS.—Pale yellow or greenish-yellow; odour faint, nutlike; taste bland, nutty.

COMPOSITION.—Contains the *glycerides of oleic, linoleic, arachidic* and *lignoceric acids.*

ACTIONS AND USES

Oleum Arachis has the actions and uses of Olive Oil, and may be used, where Olive Oil is not readily obtainable, as a substitute in official preparations.

Æthylis Oleas.—Ethyl Oleate. $C_{20}H_{38}O_2$.

CHARACTERS.—A pale-yellow oil; odour and taste disagreeable; insoluble in water, miscible with vegetable oils.

ACTIONS AND USES

Ethyl Oleate is available as an alternative to Arachis Oil as the basis of the Injections of Deoxycortone Acetate, Menaphthone, Œstradiol Diproprionate, Œstradiol Monobenzoate, Progesterone and Testosterone Propionate.

Oleum Sesami.—Sesame Oil. The oil expressed from the seeds of Sesamum indicum, N.O. Pedalineæ.

CHARACTERS.—Pale yellow; odour faint; taste bland.

COMPOSITION.—70% of *liquid fats* consisting of the glycerides of oleic and linoleic acids and 12 to 14% of *solid fats*, stearin, palmitin and arachidin; a crystalline furan, *sesamin*; and a phenol compound, *sesamol.*

ACTIONS AND USES

Sesame Oil may be used as a substitute for Olive Oil in external preparations if Olive Oil is not readily obtainable.

Oleum Gossypii Seminis.—Cotton Seed Oil. The oil from the seeds of various species of Gossypium, N.O. Malvaceæ.

CHARACTERS.—A pale-yellow oil; almost odourless; taste bland. Solid fat separates below 12° C.
COMPOSITION.—The glycerides of *oleic, linoleic, stearic, myristic* and *palmitic* acids.

ACTIONS AND USES

Cotton Seed Oil is used as a substitute for Olive Oil in external preparations, as it is cheaper.

Oleum Amygdalæ.—Almond Oil. The oil from the seeds of Prunus communis *var.* dulcis or amara, N.O. Rosaceæ.

CHARACTERS.—A pale-yellow oil; odour characteristic; taste bland, nutty.
COMPOSITION.—Glycerides of *oleic, linoleic, palmitic* and *myristic acids.*
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

Oleum Amygdalæ Volatile Purificatum.—Purified Volatile Oil of Bitter Almond (without Hydrocyanic Acid). Prepared from the cake after expressing the fixed oil from Bitter Almonds, peach or apricot kernels by distillation with water and removal of hydrocyanic acid. It consists mainly of *benzaldehyde.*

ACTIONS AND USES

Almond Oil is an external **emollient** used in skin creams and hair lotions. Internally, it is **demulcent**, nutritive and a **laxative.** Purified Oil of Bitter Almond is used as a flavour in Emulsio Olei Morrhuæ.

Acidum Oleicum.—Oleic Acid. Hydrogen Oleate. $CH_3(CH_2)_7CH{:}CH(CH_2)_7COOH$, or $C_{17}H_{33}COOH$.

CHARACTERS.—A straw-coloured liquid, insoluble in water; odour occasionally faintly rancid. It becomes semi-solid below 9° C.

ACTIONS AND USES

Oleic Acid **penetrates the skin** more readily and thoroughly than fixed oils or fats. It is therefore employed as a solvent and vehicle of active remedies, particularly alkaloids and metallic oleates, for application to the skin.

Oleum Lini.—The oil expressed from the ripe seeds of Linum usitatissimum, Flax, N.O. Lineæ.

CHARACTERS.—Yellowish-brown; odour characteristic; taste bland. Dries in air to form a hard varnish.

COMPOSITION.—The glycerides of *linoleic* and *linolenic acids* with *olein, stearin* and *palmitin.*

Linum Contusum.—Crushed Linseed. Linseed reduced to a coarse powder; recently prepared.

CHARACTERS.—A brownish-yellow powder; odourless; taste bland; contains 30% of oil and about 6% of mucilage.

ACTIONS AND USES

Externally.—Crushed Linseed is valuable as a poultice to **convey heat and moisture** to the skin and to act as a **counter-irritant.** It has the advantage of being inexpensive, and the Oil prevents it sticking to the skin. The Oil was used as a "first-aid application" to superficial burns, either alone or mixed with an equal quantity of Lime-water—so-called Carron Oil.

Internally.—An infusion of Linseed, "Linseed Tea," is a popular **demulcent** drink, and is slightly **diuretic.**

Sapo Durus.—Hard Soap. "Castile Soap." Sodium Oleate. $C_{17}H_{33}COONa$. Made by the interaction of NaOH with a suitable vegetable oil or oils or their fatty acids.

CHARACTERS.—Greyish- or yellowish-white; nearly inodorous; horny and pulverizable when dried. *Solubility.*—1 in 20 of cold, and 1 in 1·5 of hot, water; soluble in alcohol 90%.

Sapo Mollis.—Soft Soap. Potassium or Sodium Oleate. $C_{17}H_{33}COOK$.

CHARACTERS.—Yellowish-white to green; almost inodorous; unctuous. *Solubility.*—Readily soluble in water and alcohol 90%.

Preparation

Linimentum Saponis.—Soft Soap, 8%, Camphor, 4%, with Oil of Rosemary, Water and Alcohol 90%.

Sapo Animalis.—Curd Soap. Sodium Stearate. $C_{17}H_{35}COONa$. Made from NaOH and purified solid animal fats.

CHARACTERS.—Yellowish- or greyish-white; nearly odourless; horny and pulverizable when dry, plastic when warm. *Solubility.*—Sparingly in cold, but completely in hot, water; soluble in alcohol 90%.

ACTIONS AND USES

Soaps are **emollients and cleansing agents,** detaching adherent particles of dirt and loosening the superficial epithelium by lowering surface tension and dissolving the sebaceous secretions. Alcoholic (60 per cent.) or ethereal solutions (Soft Soap, 32;

Alcohol 90 per cent., 20; Ether, 52) of Soft Soap are used in surgery as cleansing agents, to remove scabs in skin diseases, and as hair-washes. Hard Soap and Curd Soap are mainly employed in making pills, plasters and liniments and for the preparation of evacuant enemata, when they or Soft Soap (2·5 per cent. solutions in warm water), by lowering surface tension, serve to disintegrate hard fæcal masses and to lubricate the rectal wall. Hard Soap is used as a detergent in dentifrices. Linimentum Saponis is a mild counter-irritant.

Paraffinum Durum.—Hard Paraffin. A mixture of solid hydrocarbons from petroleum or shale oil.

CHARACTERS.—Colourless, translucent, crystalline, inodorous and tasteless, wax-like substance; slightly greasy to the touch. M.P. 50° to 57° C.

Preparation

Unguentum Paraffini.—Hard Paraffin, 8%, White Beeswax, 2%, in White or Yellow Soft Paraffin.

Paraffinum Molle Flavum.—Yellow Soft Paraffin. "Vaseline." A mixture of semi-solid hydrocarbons, obtained from petroleum.

CHARACTERS.—A yellow, translucent, soft, unctuous mass; odourless; M.P. 38° to 56° C.

Paraffinum Molle Album.—White Soft Paraffin. A mixture of semi-solid hydrocarbons from petroleum and bleached.

CHARACTERS.—White, translucent, soft, unctuous mass; M.P. 38° to 56° C.

Paraffinum Liquidum.—Liquid Paraffin. A mixture of liquid hydrocarbons, obtained from petroleum.

CHARACTERS.—Transparent, colourless, non-fluorescent liquid; odourless and tasteless; viscosity not less than 64 centistokes at 37·8° C.

Dose.—Metric, 8 to 30 Mils; Imperial, 1/4 to 1 fl. oz.

Preparation

Emulsio Paraffini Liquidi.—Emulsion of Liquid Paraffin. Liquid Paraffin 50% with Acacia, Tragacanth, Glycerin, Sodium Benzoate, Vanillin and Chloroform in Distilled Water.

Dose.—Metric, 8 to 30 Mils; Imperial, 1/4 to 1 fl. oz.

Paraffinum Liquidum Leve.—Light Liquid Paraffin. Spray Paraffin.

CHARACTERS.—A transparent oily liquid, odourless and tasteless; insoluble in water; Viscosity not greater than 33 centistokes at 37·8° C.

ACTIONS AND USES

Paraffins do not become rancid, and, being miscible with many active drugs, are used instead of Lard as **bases for ointments** such as Lead and Zinc, or for antiseptics which are intended to produce a superficial *local* effect. They are not absorbed to any degree by the skin, and are thus not suitable bases for drugs which are meant to be absorbed. Soft Paraffin is a very common basis for ointments, and Hard Paraffin is used to give firmer consistence to soft ointments. Paraffin No. 7 (Ambrine, Burnol) consists of Resorcinol 1, Eucalyptus Oil 2, Olive Oil 5, Soft Paraffin 25, and Hard Paraffin 67, and melts at 48° C; it is sometimes applied when just melted as a protective for burns. Hard paraffin is also used to form rubefacient wax baths or sheaths for joints in physiotherapy.

Liquid Paraffin, being unabsorbed, is an excellent **lubricant and laxative** to the intestines, harmless in its effects, and much used for chronic constipation and colitis. Its disadvantage is that it may leak through the anal sphincter and soil the clothing. Emulsion of Liquid Paraffin is a pleasant form for laxative use. Some of the Paraffin is absorbed and prolonged use may cause formation of paraffinoma and also impair absorption of fat-soluble vitamins.

Sterile Liquid Paraffin is used as a protective in surgical dressings and as a catheter lubricant.

Light Liquid Paraffin, having a lower specific gravity and viscosity, is used as a solvent for Menthol, Ephedrine, Cocaine and other drugs when it is desired to apply them in the form of sprays or nebula to the nasal mucosa or throat, but its disadvantage is that it clogs ciliary movements.

Glycerinum.—Glycerin. Glycerol. A trihydric alcohol, $C_3H_5(OH)_3$, obtained by hydrolysis of fats and fixed oils.

CHARACTERS.—A clear, colourless, hygroscopic, syrupy liquid, without odour; taste sweet, followed by a sensation of warmth; miscible with water and alcohol 90% neutral.

Preparations

1. **Glycerinum Acidi Borici.**—Boric Acid, 31%; heated.
2. **Glycerinum Acidi Tannici.**—Tannic Acid, 15%.
3. **Glycerinum Amyli.**—Wheat Starch, 8·5% in Water and Glycerin, heated to form a jelly.
4. **Glycerinum Boracis.**—Borax, 12%.
5. **Glycerinum Phenolis.**—Phenol, 16%.
6. **Suppositoria Glycerini.**—Gelatin, 14, Glycerin, 70, Water, 26.

ACTIONS AND USES

Externally.—Pure Glycerin, being hygroscopic, absorbs moisture and is a slight **irritant and antiseptic** to the unbroken skin, and more so to raw surfaces. The preliminary smarting and irritation soon ceases, and Glycerin then acts as a **protective and emollient** to the skin. To avoid the irritant effect, Glycerin may be hydrated with two parts of Rose Water. It is very useful to soften the epithelium in chapped hands, cracked lips, chilblains, eczema and prurigo, and to remove scabs in skin diseases. It is largely used as a basis of cosmetic preparations, especially for skin lotions containing insoluble metallic salts, e.g. Calamina, which it helps to suspend.

Internally.—Upon mucous membranes, Glycerin is a **protective, demulcent** and **antiseptic** and assists the penetration of drugs; it is therefore used as the solvent for antiseptic or other drugs to be applied to inflamed conditions of the throat, urethra, vagina, etc. With Gelatin, it forms the basis of demulcent pastilles and suppositories. As a **sweetening agent** it is used in mixtures and occasionally in diabetic diet. It is readily absorbed and acts as a **food**. Administered as an enema (1/2 fl. oz., or 1/2 fl. oz. with 2 fl. dr. of water) or as the Suppository, Glycerin, by abstracting water from the rectal wall and acting as a lubricant and mild irritant, is a useful **evacuant** in rectal constipation or dyschezia.

Adeps.—Lard. The purified internal fat of the Hog, Sus scrofa.

CHARACTERS.—A soft, white, homogeneous, unctuous fat; odour faint, not rancid. M.P. 34° to 41° C.

COMPOSITION.—Lard consists of 60% of *olein* along with *stearin*, and some *palmitin*.

Preparation

Adeps Benzoinatus.—Benzoinated Lard. Siam Benzoin, 2% in Lard.

ACTIONS AND USES

Lard is a simple **emollient**, and forms the basis of many official ointments. Benzoinated Lard does not become rancid. Lard is absorbed slowly by the skin.

Adeps Lanæ.—Wool Fat. Anhydrous Lanolin. The purified fat of sheep's wool, freed from water.

CHARACTERS.—A yellowish, tenacious, unctuous fat; nearly inodorous. M.P. 34° to 40° C.

COMPOSITION.—It is a wax, containing the alcohols *cholesterol* and *isocholesterol* with *esters* and various *fatty acids*.

Preparations

1. **Adeps Lanæ Hydrosus.**—Hydrous Wool Fat. Lanolin. Wool Fat, 70% with Distilled Water.
2. **Unguentum Simplex.**—Simple Ointment. Wool Fat 5% with Hard Paraffin 10% in White or, if the Ointment is coloured, Yellow Soft Paraffin.

ACTIONS AND USES

Adeps Lanæ is not well absorbed but it absorbs 30 per cent. of water to form a water-in-oil emulsion—Adeps Lanæ Hydrosus. This and mixtures of Wool Fat with vegetable oils or soft paraffin form emollient creams which are absorbed together with incorporated drugs through the sebaceous glands.

Adeps Lanæ Hydrosus is a valuable **ointment basis.** It is non-irritant, absorbs water, penetrates readily and is easily absorbed but it is sticky and adherent, and difficult to saponify or wash off. It is used as a vehicle for drugs intended to be absorbed, particularly if they are water soluble.

Unguentum Simplex is also suitable for forming water-in-oil emollient creams.

Cetaceum (*not official*).—Spermaceti. A solid wax from the Sperm Whale; is an unctuous white fat, *cetin*, melting at 46° to 50° C., is emollient and used in cold creams.

Alcoholia Lanæ.—Wool Alcohols. Obtained by the saponification of the grease in sheep's wool and the separation of the fraction containing cholesterol and other alcohols; it contains not less than 28% of cholesterol.

CHARACTERS.—A golden-brown solid, brittle when cold, plastic when warm; odour faint, insoluble in water, M.P., 54° C.
COMPOSITION.—A mixture of *steroid* and *triterpene alcohols*.

Preparation

1. **Unguentum Alcoholium Lanæ.**—Ointment of Wool Alcohols. Wool Alcohols, 6, Hard Paraffin 24, White or Yellow Soft Paraffin 10, Liquid Paraffin 60.
2. **Unguentum Aquosum.**—Hydrous Ointment. Ointment of Wool Alcohols 50% in Distilled Water.

ACTIONS AND USES

Wool Alcohols, like Adeps Lanæ, form good **water-in-oil emulsions** as emollients and protectives for cosmetic purposes. They are readily absorbed by the skin and are satisfactory bases for ointments. Water-in-oil emulsions are more valuable for incorporating fat-soluble drugs, e.g., Menthol, Camphor or other volatile oils, and as emollient skin protectives, than oil-in-water emulsions, but 2·5 per cent. of Wool Alcohols may be added to the latter to improve their emollient qualities.

Alcohol Cetostearylicum.—Cetostearyl Alcohol. Lanette Wax. A mixture of solid aliphatic alcohols, chiefly stearyl and cetyl alcohols, obtained by reduction of stearic or palmitic acids, or from sperm oils.

CHARACTERS.—A white or cream-coloured unctuous mass, or white flakes; insoluble in water; M.P. not below 43° C.

Sodii et Laurylis Sulphas.—Sodium Lauryl Sulphate. $C_{12}H_{25}O.SO_2.ONa$. A mixture of sodium normal primary alkyl sulphates, chiefly sodium lauryl sulphate.

CHARACTERS.—A white or pale-yellow powder or crystals, odour slight. *Solubility.*—1 in 10 of water forming an opalescent solution.

Preparations

1. **Cera Emulsificans.**—Emulsifying Wax. Cetostearyl Alcohol 90, Sodium Lauryl Sulphate 10, Distilled Water 4.
2. **Unguentum Emulsificans.**—Emulsifying Ointment. Emulsifying Wax 30% in White Soft and Liquid Paraffin.
3. **Unguentum Emulsificans Aquosum.**—Hydrous Emulsifying Ointment. Emulsifying Ointment 30% with 0·1% Chlorocresol in Distilled Water.

ACTIONS AND USES

Cetostearyl Alcohol is used with Sodium Lauryl Sulphate to prepare Emulsifying Wax which forms **oil-in-water emulsions** readily with water to serve as cosmetic creams, or with Paraffins or fixed oils to serve as ointments. These creams or ointments mix readily with the cutaneous secretions and are absorbed without leaving a greasy surface; in them may be incorporated water-soluble drugs which are thus more effectively absorbed than from water-in-oil emulsions. They are also useful skin protectives when working with greasy materials.

Sodium Lauryl Sulphate lowers surface tension and is a detergent or cleansing agent, effective even with hard water. It is, being anionic, also a non-irritant antiseptic against Gram-negative organisms and solutions are used in surgery to cleanse the skin.

Emulsifying Wax is the basis of Cremor Penicillini and Cremor Penicillini Sterilisatus. Both Emulsifying Ointments are satisfactory bases for cosmetic or dermatological remedies.

Cera Flava.—Yellow Beeswax. Obtained from the honeycomb of the Hive Bee, Apis mellifica.

CHARACTERS.—A yellowish-brown solid; somewhat brittle when cold, becoming plastic when warm; odour agreeable, honeylike. *Solubility.*—Soluble in chloroform and in fixed and volatile oils. M.P. 62° to 64° C.

COMPOSITION.—Wax consists of *melissyl alcohol,* $C_{30}H_{61}OH$, united with palmitin to form *mellissyl palmitate* (myricin), $C_{15}H_{31}COOC_{30}H_{61}$, 80%; free *cerotic acid,* $C_{26}H_{53}COOH$; an aromatic body, *cerolein*; and *melissyl stearate.*

Preparation

Cera Alba.—White Beeswax. Yellow Beeswax bleached.

CHARACTERS.—Hard, nearly white, translucent.

USE

Wax is used only to give consistency to ointments. If given internally it is not absorbed.

Oleum Theobromatis.—Oil of Theobroma. Cacao Butter. A solid fat expressed from the roasted seeds of Theobroma Cacao, N.O. Sterculiaceæ.

CHARACTERS.—A yellowish-white solid; odour like that of cocoa; taste bland and agreeable. Melts at 29–34° C.

COMPOSITION.—Oil of Theobroma consists chiefly of *stearin*, *palmitin* and *olein*.

ACTIONS AND USES

Cacao Butter serves as a **vehicle** for more active substances in the form of lip salves, suppositories, bougies and pessaries, because it melts below the temperature of the body.

Pyroxylinum.—Pyroxylin. Dinitro-cellulose. $C_6H_8(NO_2)_2O_5$.

CHARACTERS.—White, matted filaments, like cotton-wool but is harsher to touch; highly inflammable. Readily soluble in a mixture of equal volumes of Ether and Alcohol 90%.

Preparation

Collodium Flexile.—Flexible Collodion. Pyroxylin, 2%, in Colophony, Castor Oil, Alcohol 90% and Solvent Ether.

ACTIONS AND USES

Flexible Collodion painted on the skin dries instantly by evaporation of the ether, and forms a thin film which serves as a **protective** to small wounds; it is best to place a thin wisp of cotton-wool over the part and paint over this with Collodion. It is used to prevent bedsores, seal wounds, and to close fissures or punctures made during injections. Flexible Collodion does not contract on drying, nor readily crack.

Amylum.—Starch. The starch from the grains of Maize, Zea Mays, or of Rice, Oryza sativa, or of Wheat, Triticum æstivum, N.O. Gramineæ; or of Potato Tubers, Solanum tuberosum, N.O. Solanaceæ.

CHARACTERS.—A fine, white powder, or in irregular masses readily reduced to powder; inodorous. Boiled with water and cooled, it gives a deep-blue colour with solution of iodine.

Preparation

Glycerinum Amyli.—Wheat Starch 8·5% with Water in Glycerin, gently heated. A jelly-like preparation.

ACTIONS AND USES

Externally, Starch is **protective and absorbent**, and is a common basis for Zinc Oxide, Boric Acid and Talc when used as dusting powders for tender and inflamed skins. A stiff paste made with boiling water containing 4 per cent. Boric Acid forms a useful poultice for small ulcers. The Glycerinum is an **emollient** and **protective** for skin diseases, chapped hands and chilblains. *Internally*, a mucilage (1 in 40 of water) forms a convenient **vehicle** for enemata. Starch is also an **antidote** in poisoning by Iodine, but must be followed by an emetic.

ANTISEPTICS AND PARASITICIDES

Antiseptics or **bacteriostatic agents** only arrest the growth of bacteria. **Disinfectants** or **bactericides** kill bacteria and possibly their spores. No drug, except Sulphonamides and Penicillin, which inhibits the growth of or kills bacteria is devoid of toxic action on cells or leucocytes, therefore the strengths of antiseptics must be limited to those which will not delay the natural processes of healing. Antiseptics which are also toxic to external parasites are termed **parasiticides.** An antiseptic or disinfectant action may be produced by: (1) *Physical Means*, heat, e.g. boiling, autoclaving, dry heat; or light rays of short wave-length, e.g. ultra-violet and X-rays; (2) *Increased Osmotic Tension*, e.g. Magnesium Sulphate paste and 5 per cent. Saline; (3) *Oxidizing Agents*, e.g. Peroxides, Permanganates; (4) *Reducing Agents*, e.g. Sulphur Dioxide; (5) *Drugs combining with Amines*, e.g. Hypochlorites, Chloramine, Iodine, Iodoform, Formaldehyde; (6) *Toxic Metallic Ions*, e.g. Mercuric, Silver, Zinc Salts; (7) *Protoplasmic Poisons*, e.g. Alcohol, Acetone, Boric Acid, Phenols, Cresols and Aniline Dyes; (8) *Displacing bacterial growth factor*, e.g. Sulphonamides; and (9) *Antibiotics*, e.g. Penicillin and Streptomycin. The following antiseptics have not been described previously.

Acidum Boricum.—Boric Acid. Boracic Acid. H_3BO_3.

CHARACTERS.—White, lamellar crystals or powder, unctuous to the touch, odourless; taste slightly acid and bitter. Solutions weakly acid. *Solubility.*—1 in 25 of water; 1 in 4 of Glycerin.

Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

Preparations

1. **Glycerinum Acidi Borici.**—Boric Acid 31% in Glycerin.
2. **Unguentum Acidi Borici.**—Boric Acid 10% in Paraffin Ointment, white.

Borax.—Borax. Sodium Borate. $Na_2B_4O_7,10H_2O$.

CHARACTERS.—Transparent, colourless crystals or white powder, efflorescent; taste saline, weakly alkaline. *Solubility.*—1 in 25 of water, 1 in 1 of Glycerin.

Dose.—Metric, 0·3 to 1 G; Imperial, 5 to 15 gr.

Preparation

Glycerinum Boracis.—Borax 12% in Glycerin. Reaction acid.

ACTIONS AND USES

Externally.—Boric Acid is a weak **antiseptic**, but, as it is neither irritant nor toxic to the tissues, it is particularly suitable for delicate mucous membranes. For general surgical purposes, it is employed upon wounds, ulcers, etc., as a lotion (4 per cent.), dusting powder, or in the form of Boric Acid lint and wool, either dry or as warm fomentations. In ophthalmic and aural practice, solutions of 1 to 4 per cent. are used as eye douches and for irrigation of the nasal and aural passages; a saturated solution of Boric Acid in 60 per cent. alcohol is a useful antiseptic in chronic middle-ear disease. Strengths of 1 per cent. are suitable for irrigation of the bladder, vagina, uterus and rectum.

The Glycerinum and Ointment are of service in dry **skin diseases**, while moist eczemas may be treated by dusting powders containing Boric Acid and Zinc Oxide or Calamine. Boric Acid tends to relieve itching, hence dusting powders containing it with Zinc Oxide and Starch are useful in intertrigo; they also check fetid perspiration; the Ointment relieves itching in pruritus ani and vulvæ. Borax prevents rusting of surgical instruments kept in antiseptic solutions.

Internally.—Solutions (4 per cent.) of Boric Acid or Borax, and the Glycerina (diluted with 5 or 10 parts of water) are valuable as non-toxic **antiseptic mouth washes** for stomatitis and aphthæ, and as paints or gargles in tonsillitis. Tablets containing Borax and Potassium Chlorate are used for the same conditions.

In infantile gastric catarrh, lavage of the stomach with 1 per cent. Boric Acid solution is advantageous. Taken internally, Boric Acid has little value as a gastric or intestinal antiseptic. It has been in use as a food preservative but is now discontinued because frequent doses are apt to cause gastro-enteritis. Large amounts of Boric Acid solutions left in body cavities have also caused toxic effects.

Boric Acid is excreted somewhat slowly by the kidney and is a mild **urinary antiseptic** both in acid and alkaline urines.

Liquor Hydrogenii Peroxidi.—Solution of Hydrogen Peroxide. H_2O_2.

CHARACTERS.—A colourless, odourless liquid, with a slightly acid taste; it froths with blood or saliva as it is decomposed by catalase into $H_2O + O$. It should yield 20 volumes of Oxygen.

Zinci Peroxidum.—Medicinal Zinc Peroxide. A mixture of Zinc Peroxide, Oxide and Hydroxide, containing not less than 45% of ZnO_2.

CHARACTERS.—A white, or yellowish, odourless powder; almost insoluble in water.

ACTIONS AND USES

Externally.—Hydrogen Peroxide is an active oxidizing agent and has, therefore, **antiseptic** and **deodorant** properties. It is not a powerful antiseptic because the catalase of the tissues liberates its Oxygen so rapidly that this has little time to have a lethal effect on the bacteria; but it inhibits the growth of anaerobic bacteria. The effervescence of the Oxygen, however, detaches dead tissue and bacterial debris and thus cleanses the wound. Hydrogen Peroxide is neither irritant nor toxic to the tissues and, as it is also a deodorant, it is largely used either undiluted, or more usually diluted with 5 to 10 volumes of sterilized water, as an antiseptic for wounds, sinuses, burns, ulcers, etc., and to remove scabs in skin diseases. It is also a means of removing adherent dressings painlessly. Solutions are employed as "drops" for middle-ear suppuration and conjunctivitis, and as douches for the vagina and uterus. It should be noted that there is a risk if Hydrogen Peroxide is syringed into cavities having a restricted egress; the Oxygen evolved may cause embolism or spread the infection, e.g. in the ear.

Hydrogen Peroxide is a bleaching agent used to bleach hair.

Internally.—In the mouth, Hydrogen Peroxide, diluted with 10 to 20 volumes of water, is a cleansing antiseptic mouth wash for stomatitis and gingivitis; it also bleaches the teeth but frequent use may soften the gums. As a gargle it is employed in infections of the fauces. It has been given by mouth for gastro-intestinal fermentation but is of little value.

Zinc Peroxide is bacteriostatic to anaerobic organisms and is useful, made into a paste with water, in the treatment of wounds, ulcers, burns and diabetic gangrene; it is also used for Vincent's infection of the mouth.

Sodium Perborate, $NaBO_3$, which forms Hydrogen Peroxide and the metaborate in contact with water, and **Magnesium Peroxide,** MgO_2, are used as dusting powders for wounds, and as ingredients (2–5%) of effervescing tooth powders. **Sodium Perborate**, being soluble, may be used in 2% solution as an antiseptic lotion.

Acriflavina.—Acriflavine. $C_{14}H_{14}N_3Cl,HCl$. A mixture of the hydrochlorides of 2:8-diamino-10-methyl acridinium chloride and 2:8-diamino-acridine.

CHARACTERS.—An orange-red crystalline powder; odourless; taste acid. *Solubility.*—1 in 3 of water, compatible up to 1 in 1,500 of Normal Saline; soluble in alcohol 90%; insoluble in oils and liquid paraffin.

Aminacrinæ Hydrochloridum.—Aminacrine Hydrochloride. 5-amino-acridine hydrochloride monohydrate. $C_{13}H_{10}N_2,HCl, H_2O$.

CHARACTERS.—A pale-yellow, crystalline, odourless powder; taste bitter. *Solubility.*—1 in 300 of water, 1 in 2,000 of Normal Saline, soluble in glycerin and alcohol. *p*H of 2% solution is 5 to 6·5.

Proflavinæ Hemisulphas.—Proflavine Hemisulphate. The neutral sulphate of 2: 8-diaminoacridine. $(C_{13}H_{11}N_3)_2,H_2SO_4,2H_2O$.

CHARACTERS.—An orange to red, hygroscopic, crystalline powder; odourless: taste bitter. *Solubility.*—1 in 150 of water, 1 in 50 of Normal Saline, slightly soluble in alcohol, 1 in 32 of glycerin. *p*H of 0·4% solution is 6 to 8.

Euflavina (B.P.C.).—Euflavine. Neutral Acriflavine. Neutroflavin. A mixture of 2 : 8-diamino-10-methylacridinium chloride and 2 : 8-diamino-acridine monohydrochloride.

CHARACTERS.—An orange or brownish-red powder; odour faint, taste bitter. *Solubility.*—Slightly soluble in cold, but about 1 in 4 of warm, water; 1 in 250 of Normal Saline.

ACTIONS AND USES

The acridine dye bactericides are more effective against Gram-negative organisms than Sulphonamides or Penicillin and are also toxic to Gram-positive ones. They are most commonly used in 0·1 per cent. solutions in water or Normal Saline Solution. They have a relatively low toxicity towards the tissue cells and leucocytes, and their bactericidal powers are not lowered, but somewhat increased, in the presence of serum or pus. They are not only effective in controlling sepsis in a wound, they also cleanse the wound and relieve inflammatory œdema. When used frequently, however, they do tend to delay healing, and their absorption from large surfaces has given rise to gastro-enteritis.

Acriflavine, which is somewhat acid, may cause some irritation in wounds, hence Aminacrine Hydrochloride, Proflavine Hemisulphate, or Euflavine are preferred. Aminacrine is regarded as the most effective and least toxic bactericide, but Proflavine is at present the most commonly used.

The acridine dyes are employed as lotions for wounds, burns, ulcers, etc., in strengths of 0·05 to 0·1 per cent. in water or Normal Saline Solution, and to impregnate dressings (0·1 per cent.) for "first-aid" applications or protectives. Creams (Cremor Proflavinæ N.F.) or emulsions, containing 0·1 per cent. of Proflavine and Chlorocresol with Liquid Paraffin, Beeswax, Wool Fat and Water, are satisfactory antiseptic applications for small wounds. Acridine dyes potentiate the antiseptic action of the Sulphonamides, and S.P. powder, a mixture of Sulphanilamide or, better, Sulphathiazole 99 with Proflavine 1, is an excellent antiseptic dusting powder for wounds, as it is highly active against both Gram-positive and Gram-negative organisms. Proflavine is also contained in Triple Dye for the treatment of burns.

For skin infections, e.g. impetigo and eczemas, aural boils and ulcers in the mouth, solutions (0·1 to 1 per cent.) in water, alcohol or glycerin are applied as paints; and for the conjunctiva, urethra, bladder and vagina, strengths of from 0·025 to 0·1 per cent. are suitable.

Viola Crystallina.—Crystal Violet. Medicinal Gentian Violet. Methyl Violet. Methylrosaniline Chloride. The hydrochloride of hexamethylpararosaniline. $C_{25}H_{30}N_3Cl$.

CHARACTERS.—Greenish-bronze crystals or powder; odourless. *Solubility.*—1 in 150 of water, soluble in alcohol, 1 in 30 of glycerin.

ACTIONS AND USES

Crystal or Gentian Violet is an active **antiseptic against Gram-positive organisms**; it is not irritant to the skin or mucous membranes, but has the disadvantage of its staining properties, which are greater on damaged than on healthy tissues.

For skin disinfection it is generally used along with Brilliant Green (Pigmentum Tinctorium) as a 0·5 or 1 per cent. solution of each in water or 50 per cent. alcohol, and chiefly in gynæcological practice where a non-irritant bactericide is essential. Aqueous solutions of Crystal Violet (1 per cent.) alone are also employed as paints or applications for areas infected by boils or carbuncles, and, in dermatology, for impetigo contagiosa, ringworm and infectious eczemas. **Triple Dye** or Pigmentum Violæ Crystallinæ Composita is a solution of 1 gr. each of Crystal Violet and Brilliant Green and ½ gr. of Proflavine Hemisulphate in 1 fl. oz. of water, and forms a satisfactory first-aid antiseptic for burns.

Crystal Violet is also an **anthelmintic for threadworms.** Enteric-coated pills (Pilulæ Violæ Crystallinæ) in dose of 0·06 G (1 gr.)

thrice daily are given to adults; and for children doses thrice daily of 3 mg (1/20 gr.) for each year of life. The pills are taken for 2 weekly courses with between them a week's interval without dosage; Ammoniated Mercury Ointment must be applied to the anus to obviate reinfection. Crystal Violet is also used orally for liver-fluke and Strongyloides stercoralis infestations.

In adults more than in children Crystal Violet is liable to cause headache, lethargy, vomiting and diarrhœa with griping pain.

Viride Nitens.—Brilliant Green. The sulphate of di-(*p*-diethylamino)-triphenyl-carbinol anhydride. $C_{27}H_{34}O_4N_2S$.

CHARACTERS.—Small, glistening, golden crystals, soluble in water and alcohol.

ACTIONS AND USES

Brilliant Green is used as an antiseptic mainly in association with Crystal Violet; strengths of 0·05 to 0·2 per cent. in water or Normal Saline are suitable. Ointments containing 1 or 2 per cent. are applied on small wounds and on skin infections.

THE SULPHONAMIDES

General Actions.—The Sulphonamides are active **bacteriostatic agents.** Their action depends on the fact that *p*-aminobenzoic acid is an essential factor or metabolite for bacterial growth, but if Sulphonamides, which contain a *p*-aminobenzene nucleus, are available in excess, the bacteria attempt to utilize the Sulphonamides which block the bacterial enzyme system. The Sulphonamides, by thus impairing the bacterial vitality, promote the efficiency of the defence measures of the body. The bacteriostatic power of the Sulphonamides is lowered by the presence of pus, bacterial debris, and products of tissue autolysis in a wound, therefore wounds should be surgically clean before applying a Sulphonamide; drugs containing *p*-aminobenzoic acid, e.g. Procaine, Butacaine, Orthocaine and Benzocaine, may also impair their activity if used locally along with them.

As they must be present in excess of the available *p*-aminobenzoic acid, it is important that, when used locally, a high concentration should be provided; and, when given systematically, a "loading" dose should be given to achieve quickly a blood concentration of about 10 mg per 100 Mils, and followed by doses at intervals suitable to maintain this. The rates of absorption from the small intestine and of excretion by the kidneys vary with the different Sulphonamides and determine the frequency of administration; the less absorbable Sulphonamides have a concentrated bacteriostatic action in the intestine. The absorbable Sulphonamides penetrate into all tissues of the body, including the cerebro-spinal fluid, and are present in the tissues in concentrations somewhat less than that in the blood.

During excretion by the kidney, the Sulphonamides become concentrated in the urine to about twenty times the amount in the blood, therefore large doses are not usually required for treating urinary infections. Sulphonamides are partly conjugated in the liver into **acetyl derivatives**, some of which, being only slightly soluble, particularly in acid urine, are liable to crystallize out and cause hæmaturia or tubular blockage.

The usual "loading" dose for adults with systemic infections is from 2 to 4 G (30 to 60 gr.), and this is followed by 1 G (15 gr.) at 4-, 6-, or 8-hourly intervals, depending on the rate of excretion of the Sulphonamide. The full dosage is maintained for 2 or 3 days after fever has abated and then stopped; or one-half or less of the full dose is continued for 5 to 7 days afterwards. If a Sulphonamide fails to influence a septicæmia within a week or at most 10 days, it is wise to discontinue dosage, or to observe the blood-picture carefully.

Children tolerate Sulphonamides well and are usually given one-quarter or one-third of the adult dosage during their first and second years, one-half during the third to fifth or eighth years, and thereafter full doses.

The **Sodium Compounds** of the Sulphonamides form highly alkaline solutions which can be given intravenously, but not subcutaneously, intramuscularly or intrathecally because they would cause irritation and necrosis. Their use is restricted to severe infections where it is essential to gain an immediate high blood concentration or to cases which do not tolerate Sulphonamides orally.

The susceptibility of organisms to different Sulphonamides varies to a small extent; for example, Sulphanilamide is rather more effective against streptococci, Sulphathiazole against staphylococci and E. coli, while Sulphadiazine, Sulphadimidine and Sulphamerazine are preferred and almost equally effective for pneumococcal and meningococcal infections. The organisms most sensitive to absorbable Sulphonamides in approximate relative order are hæmolytic streptococci, pneumococci, meningococci, staphylococci, gonococci, Proteus and Clostridia. Some organisms are resistant to Sulphonamides, for example S. viridans, S. fæcalis, M. tuberculosis, B. abortus, B. typhosus and paratyphosus, Rickettsias, spirochætes, protozoa and most viruses. It is important to remember that resistant strains of susceptible organisms can be developed by inadequate dosages of Sulphonamides.

Toxic Effects.—The minor toxic side-actions which may arise from the oral administration of Sulphonamides do not necessitate reduction of dosage. They were most frequent after Sulphapyridine; for this reason, it has been displaced by Sulphathiazole, Sulphadiazine, Sulphadimidine, and Sulphamerazine, which, in this order, are less liable to cause toxic effects.

Nausea and Vomiting.—This is occasional after Sulphanilamide and Sulphathiazole, but uncommon from Sulphadiazine, Sulphadimidine and Sulphamerazine; it was frequent from Sulphapyridine. It may be avoided or mitigated by giving the powdered tablets in milk, or in an alkaline mixture.

Cerebral Symptoms.—Mental confusion or apathy, drowsiness or dizziness may occur from Sulphanilamide or Sulphapyridine, but they are unusual from the other Sulphonamides.

Cyanosis.—This is most commonly seen after Sulphanilamide, but minor degrees may occur after other Sulphonamides. It is due partly to intracorpuscular methæmoglobin formation but partly also to a pigment derivative of the Sulphonamide; it is unimportant and dosage need not be reduced. If severe and accompanied by respiratory weakness, it may be due to sulphæmoglobinæmia, but this is rare: it is not provoked by sulphur-containing foods, or by Magnesium or Sodium Sulphates used as purgatives, as was once believed.

Drug Fever.—This may occur during treatment, usually in a first course between the fifth and ninth day, but in a second course it may, from sensitization, occur early.

Skin Rashes.—These may or may not accompany drug fever; they are usually of papular erythematous type and frequently itchy: not uncommonly, especially after Sulphathiazole, patients become more sensitive to sunlight, ultra-violet and X-rays.

Hæmaturia and Anuria.—This does not arise from Sulphanilamide, which forms a soluble acetyl derivative, nor from Sulphacetamide or Sulphamerazine, which are excreted in soluble forms. It arises from the crystallization as spicules in the kidney of the less soluble acetyl derivatives of Sulphapyridine, Sulphathiazole, Sulphadiazine and Sulphadimidine in this order of the relative insolubility of the acetyl compounds. This risk is obviated by giving the patient from 4 to 6 pints of fluid daily and, as the compounds are more soluble in alkaline urine, by giving Sodium or Potassium Citrate or Sodium Bicarbonate as renal antacids. The crystalline acetyl derivatives may cause hæmaturia or even anuria by blocking the renal tubules, or the ureters.

Hæmolytic Anæmia and Agranulocytosis.—Hæmolytic anæmia may occur early in susceptible persons and necessitate stoppage of treatment. Slight degrees of leucopænia are not important but should be watched as they may be the precursors of agranulocytosis, which is generally due to prolonged treatment; early indications of its onset are headache, lassitude, and sore throat. If treatment has to be prolonged for more than a week, regular blood examinations should be done.

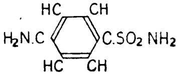
Sulphanilamidum.—Sulphanilamide. Streptocide. Prontosil Album. *p*-aminobenzenesulphonamide. $C_6H_4(NH_2).SO_2.NH_2$.

CHARACTERS.—Colourless crystals or white powder; taste slightly bitter, then sweet. *Solubility.*—1 in 250 of water, more in warm water, solution neutral.

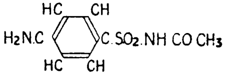
Dose.—*Initial:* **Metric, 2 G; Imperial, 30 gr.**
Four-hourly: **Metric, 1 G; Imperial, 15 gr.**

Preparation

Tabellæ Sulphanilamidi.—Usually 0·5 G.



Sulphanilamide



Sulphacetamide

ACTIONS AND USES

Externally.—Sulphanilamide, previously sterilized, is used as a dusting powder for clean wounds; it is much less effective in very septic wounds. It should be evenly distributed from a dredger over the wound, allowing about 1 G to each 10 sq. ins. up to a maximum of about 5 G. As it is soluble, it gives a satisfactory local concentration, is not irritant or toxic, and is particularly efficient against β-hæmolytic streptococci, but for staphylococcic or gas-gangrene infections Sulphathiazole or Sulphadiazine is preferable. Sulphanilamide is soon absorbed from wounds but, where a general septicæmia has developed, or is anticipated, it is best to give the drug orally as well although in somewhat reduced dosage. Local use of Sulphanilamide beyond 5 days may sensitize the skin and induce dermatitis.

Internally.—When taken orally in the form of tablets, Sulphanilamide is absorbed rapidly from the small intestine and wholly within 4 hours; the amount in the blood reaches its peak in 3 hours, and the excretion by the kidney is rapid and complete within 24 hours. It penetrates all tissues, including the cerebro-spinal fluid. A blood concentration of 10 mg per 100 Mils should be achieved by an initial "loading" dose of 2 G (30 gr.) and maintained by 1 G (15 gr.) doses at 4-hourly intervals during the 24 hours until the fever abates and for 2 or 3 days afterwards, or one-half or less of the full dose is kept up for a further 5 or 7 days.

Sulphanilamide is curative in β-hæmolytic and other streptococcal infections, but those due to S. viridans and S. fæcalis are resistant. Amongst diseases successfully treated are erysipelas and cellulitis where fever and spread abate in 2 days, puerperal septicæmia where the temperature falls by crisis, acute tonsillitis, otitis media and mastoiditis where the drug may obviate operative procedure.

For urinary infections, it is unnecessary to use a "loading" dose, as the drug is concentrated in the urine, and a daily dose of 3 G in divided amounts is adequate and usually successful in controlling coccal infections of the urinary tract and the pyelitis of pregnancy.

Maphenidum (B.P.C.).—Maphenide. Marfanil. The hydrochloride of *p*-sulphonamidobenzylamine. This is very soluble, but its bacteriostatic activity is much weaker than that of Sulphanilamide although it is not impaired by *p*-aminobenzoic acid or by pus. It is said to be more effective against gas-gangrene organisms and is applied alone or in mixtures with Sulphanilamide or Sulphathiazole as a powder to wounds. It is not used orally because it is too rapidly excreted to give an adequate blood-level.

Sulphacetamidum.—Sulphacetamide. Albucid. *p*-aminobenzenesulphonacetamide. $C_6H_4(NH_2).SO_2.NH.CO.CH_3$.

CHARACTERS.—A white or yellowish, crystalline powder; taste acid and saline. *Solubility.*—1 in 150 of water.

Sulphacetamidum Sodium.—Soluble Sulphacetamide. Sodium *p*-aminobenzenesulphonacetamide.

CHARACTERS.—A white or yellowish, crystalline powder; taste slightly bitter. *Solubility.*—1 in 1·5 of water.

ACTIONS AND USES

Externally.—Sulphacetamide Sodium solutions are not irritant and are used in the prophylaxis and treatment of ocular infections. Solutions of from 2·5 to 10 per cent. are instilled as drops to prevent infections after injuries or burns (including mustard-gas effects) and to treat conjunctivitis, blepharitis and corneal ulcers; ointments (10 per cent.) are also used.

Internally.—Sulphacetamide is excreted by the kidney in soluble form, hence there is no risk of crystalluria. It is given in doses of 2 to 4 G daily, or in an initial dose of this amount followed by 1 G 4-hourly in separated weekly courses for the treatment of urinary-tract infections with E. coli; for gonorrhœa Sulphathiazole or Sulphadiazine are better, but Penicillin is superior to all.

Sulphathiazolum.—Sulphathiazole. Thiazamide. M. and B. 760. 2-(*p*-aminobenzenesulphonamido)-thiazole. $C_6H_4(NH_2)SO_2.NH.CNS(CH)_2$.

CHARACTERS.—A white or yellowish powder, almost tasteless. *Solubility.*—1 in 2,500 of water.

Dose.—*Initial:* **Metric, 2 G; Imperial, 30 gr.**
Four-hourly: **Metric, 1 G; Imperial, 15 gr.**

Preparation

Tabellæ Sulphathiazoli.

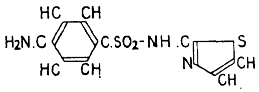
Sulphathiazolum Sodium.—Soluble Sulphathiazole. The pentahydrate of the Sodium derivative of Sulphathiazole. $C_6H_4O_2N_3S_2Na,5H_2O$.

CHARACTERS.—A white or yellowish powder, almost tasteless. *Solubility.*—1 in 3 of water.

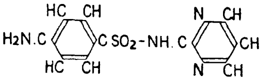
Dose.—*Initial:* **Metric, 2 G; Imperial, 30 gr.**
Four-hourly: **Metric, 1 G; Imperial, 15 gr.**
By intravenous injection:
Metric, 0·5 to 2 G; Imperial, 8 to 30 gr.

Preparation

Injectio Sulphathiazoli Sodii.—A sterile solution in Water for Injection, free from CO_2, in containers labelled with the strength in a suitable dose volume.



Sulphathiazole



Sulphadiazine

ACTIONS AND USES

Externally.—Sulphathiazole in powdered form is a very effective **bacteriostatic agent for wounds**; it is more powerful than Sulphanilamide against staphylococci and the gas-gangrene organisms. As it has less activity against Gram-positive organisms, a mixture (S.P. powder) of 99 parts Sulphathiazole with 1 part Proflavine Hemisulphate is recommended for wounds with mixed or unknown infections. In the form of an ointment, cream or paste (5 per cent.) with Zinc Oxide, it is effective in arresting skin infections such as impetigo contagiosa, sycosis and infected eczemas, but it should not be applied for more than 5 days because it can readily cause skin sensitization to light and a persistent dermatitis.

Internally.—Sulphathiazole is rapidly absorbed, an initial dose of 4 G giving a blood concentration of from 5 to 7 mg per cent. in 3 to 4 hours, but as it is rapidly excreted, subsequent doses of 1 to 2 G. should be given at 4-hourly intervals. It penetrates rather slowly into the cerebro-spinal fluid, hence is less useful in meningitis. The acetyl derivative is relatively insoluble and crystalluria has to be guarded against by giving fluids freely as well as remote antacids. Sulphathiazole does not usually produce severe toxic effects, but it is liable to cause sensitization reactions, skin eruptions and drug fever.

Sulphathiazole is more valuable in the systemic treatment of staphylococcic infections, e.g. large boils, carbuncles, cellulitis and osteomyelitis, and in infected injuries because it has a wider antibacterial range than Sulphanilamide, but Penicillin is preferable if the organisms are sensitive to it. Sulphathiazole has proved very satisfactory in the treatment of acute bronchitis, bronchopneumonia and lobar pneumonia, although one of the following three drugs is now usually preferred.

Urinary infections from E. coli, S. fæcalis and B. proteus are commonly improved by Sulphathiazole in daily dose of 3 G; Penicillin has displaced its use for gonorrhœa.

Sulphathiazole Sodium is injected in 5 or 10 per cent. solution intravenously in dose of 1 or 2 G when in serious cases it is essential to raise the blood concentration quickly.

Sulphadiazina.—Sulphadiazine. 2-(*p*-aminobenzenesulphonamido)-pyrimidine. $C_6H_4(NH_2).SO_2.NH.CN_2(CH)_3$.

CHARACTERS.—A white or yellowish powder, darkening in light; odourless and tasteless. *Solubility.*—1 in 13,000 of water.

Dose.—*Initial:* **Metric, 2 G; Imperial, 30 gr.**
Four-hourly: **Metric, 1 G; Imperial, 15 gr.**

Preparation

Tabellæ Sulphadiazinæ.

Sulphadiazina Sodium.—Soluble Sulphadiazine. The Sodium derivative of Sulphadiazine. $C_{10}H_9O_2N_4SNa$.

CHARACTERS.—A white or yellowish powder, almost tasteless. *Solubility.*—1 in 2 of water.

Dose.—*Initial:* **Metric, 2 G; Imperial, 30 gr.**
Four-hourly: **Metric, 1 G; Imperial, 15 gr.**
By intravenous injection:
Metric, 0·5 to 2 G; Imperial, 8 to 30 gr.

Preparation

Injectio Sulphadiazinæ Sodii.—A sterile solution in Water for Injection, free from CO_2, in containers labelled with the strength in a suitable dose volume.

ACTIONS AND USES

Externally.—Sulphadiazine is used, like Sulphathiazole, as a dusting powder for wounds and burns, and particularly for infections with staphylococci and gas-gangrene organisms.

Internally.—Sulphadiazine is less rapidly absorbed and more slowly excreted than Sulphathiazole, therefore by an initial dose of 2 to 4 G followed by 1 G at 4-hourly intervals, it is possible to gain the higher blood concentration of 10 to 15 mg per 100 Mils; but its penetration into the cerebro-spinal fluid is somewhat slow. Sulphadiazine is less liable to cause toxic effects than Sulphathiazole, but, although its acetyl compound is more soluble, ample fluid should be taken and renal antacids given during treatment.

Sulphadiazine is given orally in hæmolytic streptococcal septicæmias, acute bronchitis, bronchopneumonia, lobar pneumuonia and in meningococcal infections; in the latter case to accelerate the passage of the drug into the cerebro-spinal fluid, Sulphadiazine Sodium is given by intravenous injection and this may also be used in serious pulmonary cases. An initial dose of 2 G, followed by 1 G doses at 4-hourly intervals in the form of a 5 per cent. solution, is used, or it may be given by intravenous drip in 0·5 per cent. solution in Injection of Sodium Chloride. The intravenous route is discontinued when oral dosage is established.

Sulphadimidina (B.P.C.).—Sulphadimidine. Sulphadimethylpyrimidine. Sulphamezathine. Sulphamethazine. 2-(*p*-aminobenzenesulphonamido)-4 : 6-dimethylpyrimidne. $C_6H_4(NH_2).SO_2.NH.C_4N_2H.(CH_3)_2$.

CHARACTERS.—A white powder, almost odourless and tasteless. *Solubility.*—Sparingly in water.

Dose.—*Initial:* **Metric, 4 G; Imperial, 60 gr.**
Six-hourly: **Metric, 2 G; Imperial, 30 gr.**

Preparation

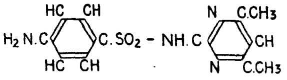
Tabellæ Sulphadimidinæ (B.P.C.).

Sulphadimidina Sodium (B.P.C.).—Soluble Sulphadimethylpyrimidine. The Sodium derivative of Sulphadimidine. $C_{12}H_{13}O_2N_4SNa$.

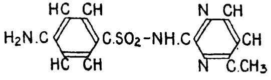
CHARACTERS.—A white powder; taste bitter and alkaline.
Dose.—*By intravenous or intramuscular injection:*
Initial: **Metric, 1 to 3 G; Imperial, 15 to 45 gr.**
Six-hourly: **Metric, 2 G; Imperial, 30 gr.**

Preparation

Injectio Sulphadimidinæ Sodii (B.P.C.) 33% in Water for Injection.



Sulphadimidine



Sulphamerazine

ACTIONS AND USES

Internally.—Sulphadimidine is rapidly absorbed and an initial dose of 4 G gives about a 10 mg per cent. peak concentration in the blood in about 3 to 4 hours, but, as it is more slowly excreted, subsequent doses of 2 G need be repeated only 6-hourly. It seldom causes nausea or other side-effects and, as its acetyl derivative is much more soluble in acid urine, it is less liable to cause hæmaturia or anuria, but fluids and renal antacids are advisable. It is much better tolerated than the previous Sulphonamides, but the blood-picture should be watched if treatment be longer than a week.

Sulphadimidine has proved equally successful with Sulphathiazole and Sulphadiazine in the treatment of hæmolytic streptococcal septicæmias, bronchitis, bronchopneumonia, pneumococcal pneumonia, and meningococcal meningitis. It is also satisfactory in pyelitis from E. coli.

Sulphadimidine Sodium may be given intravenously, or intramuscularly, as a 33·3 per cent. solution in doses of 1 to 3 G in serious cases.

Sulphamerazina (B.P.C.).—Sulphamerazine. Sulphamonomethylpyrimidine. Sulphamerizine. 2-(*p*-aminobenzenesulphonamido)-4-methylpyrimidine. $C_6H_4(NH_2).SO_2.NH.C_4N_2H_2.CH_3$.

CHARACTERS.—A white or yellow crystalline powder, darkening in light, tasteless; *Solubility.*—1 in 5,000 of water.
Dose.—*Initial:* **Metric, 3 to 4 G; Imperial, 45 to 60 gr.**
Eight-hourly: **Metric, 1 G; Imperial, 15 gr.**

Preparation

Tabellæ Sulphamerazinæ (B.P.C.).

Sulphamerazina Sodium (B.P.C.).—Soluble Sulphamerazine. $C_{11}H_{11}O_2N_4SNa$.

CHARACTERS.—A white or yellowish powder, darkening in light, taste bitter. *Solubility.*—1 in 3·5 of water.

Dose.—*By intravenous injection:*

Metric, 3 G; Imperial, 45 gr.

ACTIONS AND USES

Internally.—Sulphamerazine is also rapidly absorbed but still more slowly excreted than other Sulphonamides, hence with an initial dose of 3 to 4 G and subsequent doses of 1 G at 8-hourly intervals, it is possible to maintain a blood-level of 10 mg. per cent. or more. Toxic effects are uncommon and slight, while it has the further advantage that the acetyl derivative is very soluble in urine, hence renal antacids are unnecessary.

Sulphamerazine has an equivalent therapeutic value with Sulphathiazole, Sulphadiazine and Sulphadimidine in the treatment of streptococcal, pneumococcal and meningococcal infections, and is now largely used in place of the first two.

Sulphamerazine Sodium may be given intravenously as a 5 per cent. solution in dose of 3 G at 12-hourly intervals.

Sulphapyridina (B.P.C.).—Sulphapyridine. M. and B. 693. 2-(*p*-aminobenzenesulphonamido)-pyridine. $C_6H_4(NH_2).SO_2.NH.C_5H_4N$.

CHARACTERS.—A white or yellowish crystalline powder; taste bitter. *Solubility.*—1 in 3,000 of water.

Dose.—Metric, 1 to 4 G; Imperial, 15 to 60 gr.

Preparation

Tabellæ Sulphapyridinæ (B.P.C.).

ACTIONS AND USES

Because of its liability to produce toxic side-effects, Sulphapyridine has been displaced by the preceding four compounds.

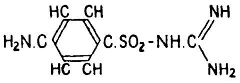
Sulphaguanidina.—Sulphaguanidine. *p*-aminobenzenesulphonylguanidine monohydrate. $C_6H_4(NH_2)SO_2.NH.C.NH.NH_2,H_2O$.

CHARACTERS.—White needle-like crystals, darkening in light, tasteless. *Solubility.*—1 in 1,000 of water.

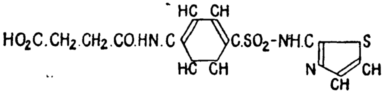
Dose.—Metric, 2 to 4 G; Imperial, 30 to 60 gr.

Preparation

Tabellæ Sulphaguanidinæ.



Sulphaguanidine



Succinylsulphathiazole

ACTIONS AND USES

Sulphaguanidine is slowly and incompletely (30 to 60 per cent.) absorbed and is, therefore, used in intestinal infections, but the amounts absorbed may cause rashes, fever and crystalluria. It has been used in doses of 3 to 4 G three or four times daily for 3 days and then twice daily in the treatment of bacillary dysentery (Shiga, Flexner, and Sonne infections), but, in view of its absorption and the dehydration associated with dysenteric diarrhœa, fluids must be given to avoid crystalluria.

Succinylsulphathiazolum.—Succinylsulphathiazole. Sulphasuxidine. *p*-2′-sulphonthiazolylamidosuccinanilic acid. $C_6H_4(NH.CO.CH_2.CH_2CHO_2).SO_2.NH.CNS(CH)_2$.

CHARACTERS.—A white or yellowish powder, darkening in light. *Solubility.*—Very slightly in water.
Dose.—Metric, 3 to 6 G; Imperial, 45 to 90 gr.

Preparation

Tabellæ Succinylsulphathiazoli.

ACTIONS AND USES

Succinylsulphathiazole is only slightly (5 per cent.) absorbed, therefore its action is confined to the intestine and it does not cause systemic side-effects. It is more efficient than Sulphaguanidine and may so reduce the intestinal bacterial flora that synthesis of the Vitamin B complex is checked; Vitamin B should be given orally to correct the deficiency.

Succinylsulphathiazole is given orally in divided doses up to 20 to 30 G or more as an initial daily dose and later in amounts of 10 to 20 G daily for bacillary dysentery (Shiga, Flexner, and Sonne infections) with very successful results. Abdominal pain and fever are relieved in 2 or 3 days and the stools become normal in 5 or 6 days, if treatment is begun early. Severe cases should also receive antidysenteric serum (Shiga).

It is also given in dose of 3 G every 4 hours as a prophylactic for 3 or 4 days prior to and after surgical operations on the colon in order to reduce the numbers and risk of E. coli, streptococcal and gas-gangrene organisms in the intestine.

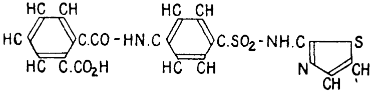
Phthalylsulphathiazolum (B.P.C.).—Phthalylsulphathiazole. Thalazole. 2-[*p*-(*o*-carboxybenzoyl)-aminobenzenesulphonamido]-thiazole. $C_6H_4(NH.CO.C_6H_4.CO_2H).SO_2.NH.CNS(CH)_2$.

CHARACTERS.—A white or yellowish-white powder; taste slightly bitter; almost insoluble in water.

Dose.—Metric, 0·5 to 2 G; Imperial, 8 to 30 gr.

Preparation

Tabellæ Phthalylsulphathiazoli (B.P.C.).



Phthalylsulphathiazole

ACTIONS AND USES

Phthalylsulphathiazole is slowly and incompletely absorbed and rapidly excreted. It is about twice as powerful an intestinal bacteriostatic agent as Succinylsulphathiazole. It is given in divided doses to the amount of 4 to 8 G daily for a week and is highly effective in checking the diarrhœa and other symptoms in Shiga, Flexner and Sonne dysentery, and in eradicating the organisms from carriers.

It is also used as a prophylactic against infection by E. coli, Cl. perfringens and streptococci before and after operations on the colon, but, as it greatly reduces the intestinal synthesis of Vitamin B, this should be given if treatment is prolonged.

THE SULPHONES

Promanide.—Promin. *p.p′*-diamino-diphenylsulphone-N,N′-didextrose-sulphonate.

Diasone.—Disodium formaldehyde-sulphoxylate-diaminodiphenylsulphone.

Promizole.—4,2′-diaminophenyl-5′-thiazolylsulphone.

Sulphetrone.—4 : 4′-bis(γ-phenyl-*n*-propylamino)diphenylsulphone-tetrasodium-sulphonate.

ACTIONS AND USES

Promanide was found to have an inhibitory action on M. tuberculosis; it is rapidly absorbed when given orally (1·5 to 3 G) but is liable to cause hæmolytic anæmia. It has been of value in 5 per cent. strengths in a Tragacanth gel for treating tuberculous abscesses and sinuses.

Promanide, Diasone and Promizole have all been used with good effects in leprosy; they appear to prevent the spread of the bacilli through the blood-stream and thus the formation of new lesions.

Sulphetrone, a cream-coloured powder, is easily soluble in water, but has a soapy taste; it is highly active against acid-fast organisms (M. tuberculosis and lepræ), is very rapidly excreted by the kidneys, becoming concentrated without crystallization in the urine. Restriction of fluid intake is desirable to maintain a blood-level of 7·5 to 10 mg per 100 Mils. Patients show a leaden-blue tint in the skin and mucosæ, not requiring reduction of dosage. It penetrates all tissues; toxic effects are mild, but by combining with the intestinal iron it causes hypochromic anæmia.

Sulphetrone in dose of 3 G by mouth daily has improved the lesions in leprosy. In moderately advanced pulmonary tuberculosis, doses of 3 G daily, given as 0·5 G tablets every 4 hours, and increased to 6 to 10 G daily has effected sufficient improvement in some cases to enable thoracoplasty to be performed and in others to arrest the progress of the disease temporarily; miliary tuberculosis and tuberculous meningitis were not benefited. Present experience indicates that its value can be adjuvant only to recognized methods of treatment.

Para-Aminosalicylic Acid.—(P.A.S.). Paramisan. Aminacyl. $C_6H_3.NH_2.OH.COOH$.

CHARACTERS.—A white, crystalline powder, sparingly soluble in water. Sodium para-aminosalicylate dihydrate is supplied as a soluble, crystalline salt and as a sterile 20 per cent. solution in 10 Mil ampoules.

Dose.—*Orally, daily:*

Metric, 15 to 30 G; Imperial, 225 to 450 gr.

ACTIONS AND USES

Para-aminosalicylic acid is used as the Sodium salt, which is given in 20 to 30 per cent. solutions in 4 daily doses of 3 to 5 G at 2½- to 3-hourly intervals, omitting night dosage, for a course of 1 to 3 months; its bitter taste is partially masked by Syrup of Orange or Peppermint Water.

Para-aminosalicylic acid was found *in vitro* to have an active inhibitory effect on M. tuberculosis. The Sodium salt is rapidly absorbed, attains a blood-level of about 7 mg. per 100 Mils in an hour, but this concentration falls quickly because excretion by the kidney is rapid, mainly within two to six hours. Unless well diluted and flavoured, it is nauseating and may also cause diarrhœa, but not other toxic effects.

Para-aminosalicylic acid is on clinical trial in tuberculosis. Favourable results are reported from a 10 per cent. solution applied locally in tuberculosis of the skin, and from 20 per cent. solutions injected locally in tuberculous fistulas, empyemas and glands. In pulmonary tuberculosis, it controls the pyrexia and cough, reduces the numbers of bacilli in the sputum, increases appetite and weight, and improves the general condition; but radiological improvement is usually slight in all except recent exudative disease in which fibrosis may be promoted. Improvements have also been reported in intestinal and renal tuberculosis. Its position at present is that of a non-toxic agent which, in association with bed-rest and sanatorium treatment, may, in some cases, promote such improvement as to render thoracic surgery possible.

It has proved very valuable when given orally along with Streptomycin injections by delaying or inhibiting the development of Streptomycin-resistant strains of the tubercle bacillus.

Thiosemicarbazones.—Thioparamizone. TB 1/698. 4-acetylaminobenzaldehyde thiosemicarbazone. Thioparamizone is issued in 50 mg. tablets. *Dose.*—Orally: 12 to 50 mg daily, gradually increased. The thiosemicarbazones are bacteriostatic to the tubercle bacillus and may prove useful as adjuvants to Streptomycin in acute exudative types of pulmonary tuberculosis, and initial favourable results are reported in tracheal, laryngeal and urinary tuberculosis. Side-effects are nausea, skin rashes, and, rarely, leucopenia.

ANTIBIOTICS

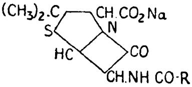
Penicillinum.—Penicillin. The Sodium or Calcium salt of the antimicrobial acid produced when Penicillium notatum or related organisms are grown under appropriate conditions on or in a suitable medium.

CHARACTERS.—Pure Sodium Penicillin is a white powder in crystals, granules or scales; and Calcium Penicillin is a white amorphous powder. When incompletely purified, they are pale-yellow to light-brown, amorphous, hygroscopic powders. *Solubility.*—Easily soluble in water (solution of 20,000 Units per Mil has a *p*H of 5·0 to 6·5), insoluble in fixed oils and liquid paraffin.

Penicillin must comply with tests for undue toxicity and absence of pyrogens and be assayed biologically for potency in inhibiting the growth of a sensitive strain of staphylococcus in comparison with the Standard Preparation. Penicillin salts are dispensed in sealed containers, labelled to show (1) if it is Sodium or Calcium Penicillin, (2) the total number of Units in the container, and (3) the minimum number of Units per mg, and are kept at a temperature below 15° C. The International Unit is 0·65 microgramme of the Standard International Sample of the pure Sodium Salt of Penicillin II (or G). A mega-Unit is 1,000,000 Units.

Five Penicillins are known at present: I (or F.), II (or G.), III (or X.), and Amylpenicillin, which differ little in activity, and Penicillin IV (or K.) which is less active *in vitro* and more rapidly destroyed in the body.

Dose.—Determined by the physician in accordance with the needs of the patient.



Penicillin

$\triangle^2$-Pentenyl-penicillin I (or F.)	$R = CH_2.CH : CH.CH_2.CH_3.$
Benzyl-penicillin II (or G.)	$R = CH_2.C_6H_5.$
p-hydroxybenzyl-penicillin III (or X.)	$R = CH_2.C_6H_4.OH.$
Amylpenicillin	$R = (CH_2)_4.CH_3.$
Heptylpenicillin IV (or K.)	$R = (CH_2)_6.CH_3.$

Preparations

1. **Injectio Penicillini.**—Injection of Penicillin. A sterile solution of Sodium or Calcium Penicillin (usually 50,000 Units per Mil) in Water for Injection, prepared by dissolving the Penicillin from a sealed container in the requisite amount of Water for Injection. It should be used within 7 days of preparation and be kept below 4° C. A container of multiple doses has a suitable bacteriostatic added.

Dose.—Determined by the physician in accordance with the needs of the patient.

2. **Injectio Penicillini Oleosa.**—Oily Injection of Penicillin. A suspension of Calcium Penicillin (usually 125,000 Units per Mil) in White Beeswax 4·5 and Arachis Oil or Ethyl Oleate to 100 **for intramuscular injection only.** Labelled with the name, the number of Units in a suitable dose volume and which base is used.

Dose.—Determined by the physician in accordance with the needs of the patient.

3. **Cremor Penicillini.**—Penicillin Cream. Sodium or Calcium Penicillin (usually 500 Units per G) in Emulsifying Wax, Hard and Liquid Paraffins, Chlorocresol and Distilled Water; freshly prepared as it loses potency on keeping.

4. **Cremor Penicillini Sterilizatus.**—Sterilized Penicillin Cream. Sodium or Calcium Penicillin (usually 500 Units per G) in Emulsifying Wax, Hard and Liquid Paraffins and Distilled Water, the base being first sterilized; freshly prepared as it loses potency on keeping.

5. **Unguentum Penicillini.**—Penicillin Ointment. Calcium Penicillin (usually 500 Units per G) in Ointment of Wool Alcohols; protect from moisture and store below 15° C.

6. **Oculentum Penicillini.**—Penicillin Eye Ointment. Calcium Penicillin (usually 1,000 Units per G) in Yellow Soft Paraffin and Wool Fat: should be used soon and stored below 15° C.

7. **Trochisci Penicillini.**—Penicillin Lozenges. Calcium Penicillin

(usually 500 Units in each 1 G lozenge) in Sucrose or Lactose with suitable binding agents.

ACTIONS AND USES

Penicillin is a bacteriostatic, or in sufficient concentration a bactericidal, agent against particular organisms. Its effect is on the dividing organisms which swell, do not divide, and disintegrate; probably it prevents the passage through the cell wall of glutamic acid which is required for the synthesis of protein. Its action is not impaired by *p*-aminobenzoic acid, pus, serum, bacterial debris or products of tissue autolysis. It is inactivated by excess of acid or alkali (although stable between *p*H 5·0 and 8·0), by heat (if moist), oxidizing agents, alcohols, ketones, cysteine, heavy metallic salts, and by penicillinase, an enzyme formed by Gram-negative organisms, e.g. E. coli and B. subtilis. Solutions in water of 20,000 to 25,000 Units per Mil are isotonic.

Penicillin is harmless to leucocytes and tissue cells; its speed of action depends on the susceptibility of the organism and up to a limit on the concentration of the Penicillin. Sensitive streptococci and staphylococci succumb to strengths of 0·001 Units per Mil, whereas E. coli requires 31 Units per Mil. In wounds, for which solutions of from 1,000 to 5,000 Units per Mil are usually adequate as antiseptics, resistant organisms, e.g. Ps. pyocyanea (æruginosa) commonly survive. In systemic treatment also the different sensitivity of organisms modifies the clinical usage, thus the gonococcus may be eradicated by 150,000 Units in a day, whereas syphilis requires at least 2·5 to 3 mega-Units during a week and Str. viridans in endocarditis requires at least 14 mega-Units during a month. It is, therefore, important to know which organisms are sensitive to Penicillin and, in unknown infections, the organism should be identified bacteriologically.

Sensitive Organisms: Streptococcus pyogenes and viridans, also some anaerobic streptococci; *Staphylococcus* aureus; *Diplococcus* pneumoniæ; *Neisseria* gonorrhœæ, meningitidis, and catarrhalis; *Clostridium* tetani, perfringens (welchii), septicum, œdematiens, and botulinus; *Bacillus* anthracis and subtilis; *Corynebacterium* diphtheriæ; *Spirochætæ* of syphilis, yaws, relapsing fever, Vincent's angina and Weil's disease; *Spirillum* minus (rat-bite fever); *Actinomyces* bovis; *Micrococcus*; and *Sarcinæ*. Larger viruses (psittacosis, ornithosis) and Rickettsiæ are partially sensitive.

Insensitive Organisms: Streptococcus fæcalis; *Bacterium* (E.) coli, typhosum, and paratyphosum, Shigæ, Flexneri, and Sonnei;

Vibrio choleræ; *Proteus* vulgaris; *Bacillus* Friedländer; *Pseudomonas* æruginosa (pyocyanea), and fluorescens; *Hæmophilus* influenzæ (some sensitive) and pertussis; *Mycobacterium* tuberculosis, paratuberculosis and lepræ; *Pasteurella* pestis and tularensis; *Brucella*; Monilia; moulds; yeasts; and most viruses.

The common organisms most sensitive to Penicillin in approximate relative order are gonococci, meningococci, streptococci, staphylococci, pneumococci, treponema pallidum, clostridia, and anthrax. Organisms do not readily develop strains resistant to Penicillin in the body.

Absorption and Excretion.—Penicillin is rapidly absorbed from raw tissues, from intramuscular injections and from the duodenum and upper small intestine, but about 60 per cent. or more is destroyed by the acid in the stomach. Given intramuscularly, the maximal blood concentration is reached in 30 minutes; it penetrates all tissues but little enters the cerebro-spinal fluid.

Penicillin is rapidly excreted through the renal tubular epithelium and, given intravenously, about 15,000 Units disappear from the blood in an hour or, given intramuscularly, in 2 hours; therefore large doses (30,000 to 50,000 Units by intramuscular injection) are necessary every 3 hours to maintain adequate therapeutic blood concentrations which should be above 0·06 Unit per Mil. Small amounts are excreted in the saliva and bile.

When Penicillin is applied locally to a wound, it is rapidly absorbed and inhibitory concentrations are found in the blood so that local treatment affords some general protection. In order to delay local absorption from intramuscular injections and thus to prolong the blood concentration, the Injectio Penicillini Oleasa is employed; by its use dosage can be spaced to 1 or 2 injections daily.

Procaine-Penicillin.—This is a relatively insoluble, equimolecular combination, containing 300,000 Units Penicillin with 0·12 G Procaine in 1 Mil, which, when injected suspended in Arachis Oil, is slowly absorbed and gives adequate blood-levels of Penicillin up to 24 hours from a dose of 300,000 Units. Procaine-Penicillin with 2 per cent. Aluminium Stearate in Arachis Oil gives a greater prolongation of action, especially if the particles of the suspension are fine. This preparation has a rapid initial absorption, giving serum Penicillin levels from 300,000 Units of above 0·2 Unit per Mil from 1 to 3 hours after injection and levels of 0·06 Unit per Mil or more for at least 48 hours. Daily or alternate day injections maintain a continuous Penicillin level in the blood. Procaine-Penicillin causes no undesirable reactions, is comparatively free from irritation or pain, and daily injections suffice to maintain a high Penicillin blood-level.

Distaquaine is crystalline Procaine-Penicillin II (or G) with a suspending agent, issued in dry form in phials containing 300,000 and 900,000 Units. Sterile distilled water, isotonic Saline, or Glucose solution is added and the phial shaken to form a watery suspension. A single dose of 300,000 Units is stated to maintain an adequate blood-level for 24 hours.

Oral administration of Penicillin in doses of 4,000 Units per lb. body weight in 24 hours has proved effective in children under six months in whom the gastric acidity is low. By giving Penicillin on an empty stomach in 4 fl. oz. of 5 to 10 per cent. Glucose solution, containing 1 G of Sodium Bicarbonate or Sodium Citrate (0·5 G per 20,000 Units) as a buffer, satisfactory blood-levels are attained by doses about 5 or 10 times greater than the intramuscular dosage; for maintenance doses from 100,000 to 500,000 Units are required at 3-hourly intervals.

Toxic Effects from Penicillin are practically absent except that allergic reactions, usually from sensitization by a previous dose, such as erythematous itching eruptions, muscular and joint pains, and asthmatic attacks, may occur; they are relieved by antihistaminic drugs.

External Uses.—Penicillin is used for the treatment of infected wounds and burns in the form of sterile dusting powders containing 1,000 to 5,000 Units of Calcium Penicillin per G, in pastes, or in solutions of similar strength. Mixtures of Penicillin and Sulphonamides may be used in mixed infections.

The Creams and Ointment are used for superficial skin infections and are effective in impetigo contagiosa, sycosis and septic eczemas. The Oculentum is suitable for conjunctival and corneal wounds and infections; recently, pure Penicillin (25,000 Units) has been injected in 0·5 Mil of 0·5 Procaine solution subconjunctivally with success in hypopyon ulcer. Penicillin Lozenges are of value in oral infections, but they are not specific for Vincent's angina; they are useful prophylactics against infection following extraction of teeth. They should be allowed to dissolve slowly in the mouth and be replaced every 2 hours, but may cause stomatitis.

Dosage for Systemic Use.—Penicillin was given at first by continuous intravenous or intramuscular drip. It is now given mainly by intramuscular injection which with purer products is painless.

The official Injection contains 50,000 Units per Mil, unless otherwise ordered, but it is common to use solutions for injection containing 100,000 to 500,000 Units per Mil. The sites selected for injection are the buttock, thigh, deltoid or abdominal muscles. The following is a general guide for average treatment:

Intramuscular Injection in Solution: 50,000 Units every 3 hours; 100,000 Units every 6 hours; 250,000 Units twice daily; or 500,000 Units once daily.

Injectio Penicillini Oleosa: 300,000 Units twice, or 600,000 Units once daily. Procaine-Penicillin with Aluminium Stearate in Oil, 300,000 Units daily.

Orally: 200,000 Units initially, and 100,000 Units at least every 3 hours, on an empty stomach.

Systemic Uses.—Penicillin is now used largely as a **prophylactic** against general infections and is given prior to operations on septic foci or to extraction of septic teeth; a dose of 50,000 Units 2 or 3 hours before, and another immediately before, operation, followed by 2 or 3 further doses, are regarded as sufficient unless complications arise; or one large initial dose of Procaine-Penicillin.

In acute infections, it is now usual to treat the case with Penicillin at once, but if no fall in temperature or relief of symptoms is gained in 24 hours it is advisable to have the susceptibility of the organism tested. Surgical treatment must be carried out where necessary, e.g. in osteomyelitis, abscess formation, etc. Acute cases should be treated by intramuscular injection, not by oral dosage.

The clinical conditions in which Penicillin, given systemically, is of great value and commonly curative include septic wounds and burns, boils, carbuncles, compound fractures, whitlows, cellulitis, osteomyelitis, periostitis, teno-synovitis, puerperal and other septicæmias, tonsillitis, Vincent's angina, otitis media, mastoiditis, broncho-pneumonia, lobar pneumonia, empyema, peritonitis, pericarditis and meningitis. In pulmonary infections, inhalations from a nebulizer of vapour containing 200,000 or more Units have also been used with success.

For meningococcal or other non-tuberculous meningitis, in addition to systemic injections, pure crystalline Penicillin should be given intrathecally or intracisternally in dosage of 50,000 to 100,000 Units dissolved in 2 to 4 Mils of Water for Injection.

Gonorrhœa is usually cured by the injection of 100,000 to 200,000 Units in three doses at about 8-hourly intervals, or by a single massive dose of 500,000 Units in the form of the Oily Injection, or Procaine-Penicillin. It should be noted that with the rapid cure of a gonococcal infection, a simultaneous syphilitic infection may be masked and gonorrhœal cases should be kept under observation.

In syphilis, the Treponema pallidum disappears from the superficial lesions within 24 hours after a single (50,000 Units) dose of Penicillin and infectivity is checked, but it is now considered that, although an initial week's treatment with Penicillin to a minimum total of 2·5 to 5 mega-Units produces an apparent cure, relapses are very frequent, and it is advisable to combine Penicillin therapy with courses of Organic Arsenicals and Bismuth. Details of syphilitic treatment are given on p. 101. It is considered that a synergistic or potentiating effect is gained from the use of the three drugs, but the use of the Organic Arsenicals and Penicillin in conjunction too early may lead to severe endotoxic reactions. Some clinics start treatment with Neoarsphenamine or Oxophenarsine and Bismuth, and substitute about the third week daily doses of 500,000 Units of Penicillin. In treating syphilis of more than two years' duration, Penicillin must be used with care because of its liability to cause endotoxic or Herxheimer reactions; in cardio-vascular syphilis also it should be commenced in small (30,000 Unit) doses of the Oily Injection, and gradually increased.

In neurosyphilis, Penicillin in single doses of 500,000 Units daily to a total of 6 mega-Units is displacing the use of Tryparsamide.

Subacute bacterial endocarditis (Str. viridans) requires daily dosage with at least 0·5 mega-Unit for 28 days; this will control the infection in 90 per cent. of cases which, however, should be kept under observation as relapses are common.

Agranulocytosis of various ætiology is often greatly benefited by Penicillin therapy which should be commenced as soon as possible in full dosages and the effects observed by blood counts.

Streptomycin.—An antibacterial agent derived from strains of Streptomyces griseus, when grown on a suitable medium.

CHARACTERS.—Streptomycin base is crystalline. It is used as the very soluble Hydrochloride, Sulphate or Calcium Chloride double salt; as a mixture of the latter two precipitates calcium sulphate, a change from one to the other of these salts should be avoided or separated by several weeks' interval. The base and salts are fairly stable if kept below 15° C., or, if in solution, in a refrigerator, but solutions are best freshly prepared.

Dose.—*Intramuscularly, daily:*
Metric, 1 to 2 G; Imperial, 15 to 30 gr. (up to 20 mg per lb. body weight).
Intrathecally, daily:
Initial **50 to 100 mg**; maintenance **25 to 50 mg.**

For intramuscular injection, solutions of 100 to 200 mg per Mil are used in Water for Injection or Sterile Saline; for intrathecal injections, 100 mg in 5 or 10 Mils of Sterile Saline.

ACTIONS

Streptomycin is bactericidal against many organisms, including Penicillin-resistant species such as B. proteus, Brucella abortus, E. coli, Eb. typhosus, H. influenzæ, Past. tularensis, Ps. pyocyanea (æruginosa), and My. tuberculosis; but resistant strains are liable to develop during treatment.

If given orally, little is absorbed, but 2 to 3 G daily act as intestinal bactericides and have been given with success before colonic operations and in infantile gastro-enteritis.

When injected intramuscularly, the maximum blood-level occurs in from 1–3 hours and decreases during the next 10 or 12 hours; it reaches all tissues but very little enters the cerebro-spinal fluid. It is excreted within 24 hours, mainly in the kidneys; small amounts appear in the bile, pleural, pericardial, and ocular fluids. Injections were advised originally at 3-hourly intervals as it was thought to be bacteriostatic only, but, as it is bactericidal, 2 injections daily are now regarded as satisfactory in most cases. Intravenous injection has no advantages.

Therapeutic Uses.—For local application to wounds, sinuses and fistulæ, strengths of 25 to 50 mg per Mil are advised but even 2 mg per Mil is stated to be effective.

Intramuscular treatment has proved successful in tularæmia, in bacteræmia from E. coli and Ps. pyocyanea, in peritonitis, in pulmonary infections with B. Friedländer, and in otitis media. In bacilluria, particularly from Proteus vulgaris, Str. fæcalis, E. coli and Ps. pyocyanea, the general results are good, but intensive, brief treatment (e.g. 3 G in 4 doses daily for 2–3 days) is desirable owing to the rapid development of organismal resistance. It is also valuable in meningitis from H. influenzæ and other Penicillin-resistant organisms.

Streptomycin is the most effective drug known for miliary and meningeal tuberculosis in daily intramuscular doses up to 2 G for at least 4 to 6 months; in meningeal cases, 50 to 100 mg are also given intrathecally for the first few weeks and then on alternate days, or in half this dose, for two more weeks.

In other tuberculous diseases, 1 G (or 10 mg per lb.) daily by one or two intramuscular injections is probably equally effective and is less toxic. The maximal effect is reached in 1 or 2 months; treatment for more than 3 months is useless and may be dangerous. The development of resistant strains (usually from about the fifty-third day) limits the duration of an effective dosage and may prevent its useful repetition, while cases with sputum will disseminate resistant strains. The simultaneous oral administration of Para-aminosalicylic acid retards or inhibits the development of resistant strains of M. tuberculosis.

In pulmonary tuberculosis, the present indications for Streptomycin are for progressive lesions of recent development, which are unlikely to benefit from bed-rest and/or collapse therapy alone, including rapidly advancing cases, in whom collapse therapy would be inadvisable, and cases of acute spread even after collapse therapy. For minimal early lesions with hopeful prognosis, old chronic fibroid or fibro-caseous lesions and terminal conditions, it is not advised. Improvement occurs in the temperature, weight, sedimentation rate, bacillary content of the sputum, and radiologically, but clinical cure is not achieved; the drug may so improve the patient's condition that collapse therapy or thoracic surgery may become practicable. In thoracic surgery, its prophylactic use to cover thoracoplasties is not advised, but it is probably of value before and after lung resections, and its injection locally into infected intrapleural spaces is useful. It is also used for the treatment of spreads.

Ulcerative lesions of the trachea and bronchi respond well; intestinal and peritoneal tuberculosis improve symptomatically but relapses are common; in some types of renal tuberculosis, improvement and temporary arrest have been obtained. It cannot replace surgery in joint or bone tuberculosis.

Toxic Effects.—Local pain and induration from injection is not severe and is reduced by Procaine. The risk of toxic effects increases with age but it is now much less with purer products and lower dosage. Headache, flushing of the skin, syncope and erythematous or papular rashes may occur early. Nausea, vomiting and anorexia, relieved by antihistamic drugs, may begin about the third week. Tinnitus, vertigo and deafness from vestibular dysfunction, is a common sequel and may be transient or permanent; this must be considered as a risk of the prolonged treatment in meningitis cases. Sensitization, causing eczematous skin eruptions, has occurred after some months in attendants who should wear rubber gloves when handling the drug.

Dihydrostreptomycin Sulphate.—Dose.—*Orally:* 0·5 to 1 G daily; *intramuscularly:* 1 to 3 G daily; *intrathecally:* 0·05 to 0·1 G; as an injection 1 G is dissolved in 4 Mils of Water for Injection. It is about equal in therapeutic activity to Streptomycin and is less liable to produce toxic effects. It is used for the same conditions as Streptomycin.

Chloramphenicol.—Chloromycetin. *l*-ψ-1*p*-nitrophenyl-2-dichloroacetamidopropane-1: 3-diol.

Chloromycetin is derived from cultures of Streptomyces venezuelæ and has been obtained as slightly soluble crystals; it has also been synthesized.

Dose.—*Orally*: **4 to 6 G** daily (initial, **4 G** followed by **0·25 G** at 2-hourly intervals) or **50 mg per Kg** body weight, initially.

ACTIONS AND USES

Chloramphenicol is active when given orally; it is rapidly absorbed and excreted. A dose of 2 G gives a blood-level of 10 microgrammes at 2 hours and 5 microgrammes at 8 hours afterwards; its toxicity is low, but injections are irritant. Organisms do not appear to become resistant to it.

It has been successful in treating relapsing fever, typhoid, typhus, scrub typhus and lymphogranuloma inguinale, as well as infections with B. Friedländer and E. coli.

Aureomycin.—Duomycin. This antibiotic is derived from a strain of Streptomyces aureofaciens and is used as a yellow, crystalline, soluble hydrochloride (acid).

Dose.—*Orally*, daily: **0·6 to 3·5 G** (10 to 60 mg per Kg body weight) in four portions.
Intramuscularly, daily: **10 to 20 mg** in sterile saline.

ACTIONS AND USES

Aureomycin is bacteriostatic rather than bactericidal. Sensitive organisms are Hæmolytic streptococci, Str. fæcalis, D. pneumoniæ, Staphylococci, E. coli, H. influenzæ, Brucella suis and abortus, Rickettsias and certain viruses (e.g. psittacosis and lymphogranuloma inguinale); Ps. pyocyanea, and Proteus are resistant.

Very favourable results are reported in typhoid, typhus, Rocky Mountain fever, brucellosis and in urinary infections with E. coli. Aureomycin Borate (0·5 to 1 per cent., solution) is not irritant and has given good results in ocular infections.

Toxic Effects are nausea, vomiting and diarrhœa, but they are usually transitory: large doses may cause a fever and syncope.

Terramycin from Streptomycin rimosus is crystalline and has actions similar to aureomycin. *Dose.—Orally*: 1 to 2 G daily, divided into 6-hourly doses. It has proved effective in pneumonia, whooping cough, urinary infections from E. coli and Gonococcus.

Liquor Formaldehydi.—Solution of Formaldehyde. "Formalin." H.COH. Contains 37% to 41% of Formaldehyde in water.

CHARACTERS.—A colourless liquid; odour characteristic, pungent; taste burning. Miscible with water.

ACTIONS AND USES

Externally.—Formaldehyde is an **antiseptic** in strengths of 1 : 1,000 to 1 : 2,000; the action is due to its reduction and uniting with the amino groups of proteins which it coagulates. As a vapour produced by sprays, it is a good **room disinfectant** as it does not bleach fabrics. Solutions (10 per cent.) are used as disinfectants for floors, etc., and excrement, and (1 to 2 per cent.) as antiseptics for instruments and to harden catgut; it is too irritant for wounds, but may be used as a caustic and to harden the skin, for soft corns; solutions (10 per cent.) in Glycerin have been used with benefit in ringworm, lupus and dry eczema.

Internally.—It is employed in 0·5 to 1 per cent. dilutions as a **mouth wash**, or with Glycerin as a **gargle** for stomatitis and tonsillitis, and as a paint for laryngitis. Tablets containing Paraform 1/4 gr. and Peppermint Oil are employed for sore throat.

Cetrimide.—Cetavlon. A mixture of alkyl ammonium bromides containing about 75% of $C_{16}H_{33}(CH_3)_3N.Br$.

ACTIONS AND USES

Cetrimide is used as a cleansing agent and bacteriostatic in 1 per cent. aqueous solutions which are not irritant or toxic. It greatly lowers surface tension and detaches debris, crusts and scabs in wounds and skin infections; its antiseptic power lasts, when dried on the skin, for some hours. It is largely employed to cleanse the skin before operations, to clean dirty wounds and burns, and to keep instruments aseptic.

Alcohol Benzylicum.—Benzyl Alcohol. $C_6H_5.CH_2OH$.

CHARACTERS.—A colourless, almost odourless liquid, taste burning. *Solubility.*—1 in 25 of water.

ACTIONS AND USES

Benzyl Alcohol is an antiseptic and local anæsthetic which is not toxic or irritant. It is occasionally used in dentistry for sensitive dentine and in dermatology as an ointment (10 per cent.) for pruritus. In Ethanolamine Oleate Injection, it relieves pain.

Propamidine Isethionate is an antiseptic which is not inhibited by pus or *p*-aminobenzoic acid and is stated to be active on organisms which have resisted Sulphonamides. Creams or jellies (0·15%) are employed, but, if used for more than a week, they may cause superficial necrosis.

Phenol.—Phenol. Carbolic Acid. C_6H_5OH.

CHARACTERS.—Colourless, needle-like, deliquescent crystals; odour peculiar, not tarry; taste sweetish, pungent. *Solubility.*—100 parts are liquefied by 10 parts of water, and form a clear liquid with 30 to 40 parts of water. Completely soluble 1 in 13 of water (faintly acid); freely soluble in alcohol 90%, glycerin, and in fixed oils. Solutions give deep purple with Fe_2Cl_6.

Preparations

1. **Phenol Liquefactum.**—Liquefied Phenol. "Liquefied Carbolic Acid." Phenol 80% in Water. A colourless liquid, becoming pinkish. Forms a clear solution on addition of 15 parts of water.
2. **Glycerinum Phenolis.**—Glycerin of Phenol. Phenol, 16% in Glycerin. Dilute with Glycerin but *not* with water.
3. **Suppositoria Phenolis.**—60 mg (1 gr.) in each, with Oil of Theobroma.
4. **Trochisci Phenolis.**—30 mg (1/2 gr.) of Phenol in each.
5. **Unguentum Phenolis.**—Phenol Ointment. Phenol 3% in white beeswax, lard, hard and soft paraffins.

ACTIONS AND USES

Externally.—Phenol is a **protoplasmic poison.** It also **precipitates proteins**; but, as it forms no compound with albumin, it continues to diffuse into the tissues. For these reasons it is a powerful and penetrating **antiseptic.** In 1 per cent. aqueous solutions Phenol is toxic to bacteria, and 0·2 per cent. strengths will inhibit their growth; but much stronger concentrations (5 to 10 per cent.) are required to destroy spores. Phenol loses about 10 per cent. of its activity in presence of organic matter.

Strong solutions on the skin, mucous or raw surfaces cause brief tingling and burning, followed, owing to a paralysis of the sensory endings, by **numbness and local anæsthesia**; the superficial cells become white and shrunken owing to protein precipitation and, if the action continues, necrosis of the tissues will be produced; solutions even of 1 per cent. strength, applied as wet dressings, may by penetration cause deep **gangrene** in peripheral parts without pain being perceived. Phenol or Liquefied Phenol is a **powerful caustic.**

As an **antiseptic** Phenol is used in 0·5 to 1 per cent. solutions for general surgical purposes, such as cleansing the skin, for septic wounds, and for surgical instruments. On account of its toxicity to cells and the danger from absorption it is much less used than formerly, and should not be employed for injection into septic cavities. As a caustic, Liquefied Phenol is occasionally employed to touch small warts, boils, etc. For its local anæsthetic and antiseptic effects it is applied in ringworm, sycosis, pityriasis and pruritus. Crude Liquefied Phenol (containing cresol) is much used as a disinfectant for stables, utensils and closets.

Internally.—The vapour of Phenol from an inhaler (20 min. in a pint of hot water) is a sedative to the throat and bronchi. Glycerinum Phenolis is used as a paint for tonsillitis and sore throat; it should be diluted with Glycerin, *not* with water, which makes it caustic. The Trochiscus is used in septic tonsillitis and pharyngitis.

Actions after absorption.—Phenol is readily absorbed from the skin and mucous surfaces. Toxic absorption of Phenol causes headache, a brief stage of motor stimulation, followed by muscular weakness, cerebral depression, circulatory collapse and unconsciousness.

Excretion.—Phenol is rapidly excreted in the urine, partly unchanged, largely as ethereal sulphates or with glycuronic acid; and partly oxidized to hydroquinone or pyrocatechin, which by further oxidation impart to the urine an olive-green to brown colour, becoming darker on standing.

Cresol.—Cresol. Cresylic Acid. A mixture of cresols, $CH_3C_6H_4OH$, and other phenols, obtained from coal tar.

CHARACTERS.—A straw-coloured liquid, becoming brown on keeping; odour phenolic and tarry. *Solubility.*—1 in 50 of water, solution neutral, taste pungent; freely in alcohol 90%; in glycerin and in fixed and volatile oils. Aqueous solution gives transient bluish colour with Fe_2Cl_6 solution.

Preparation

Liquor Cresolis Saponatus.—Solution of Cresol with Soap. Lysol. Cresol 50% with Linseed Oil and Potassium Hydroxide in Water.

ACTIONS AND USES

Externally.—Cresol is three or four times more **powerfully antiseptic** than Carbolic Acid, but is less toxic and caustic. It loses, however, 50 to 70 per cent. of its power in contact with organic matter. It is used in 0·25 to 1 per cent. solutions as a general antiseptic. The Solution with Soap, 1 to 2 per cent. in water, is an excellent cleansing antiseptic but renders the hands and instruments slippery. Many proprietary preparations of Cresol are available, e.g. Acrosyl, Creolin, Cyllin, Izal, Jeyes' Fluid, Kerol, Monsol, Trikresol, but they have little, if any, advantage over Cresol. Amyl-meta-cresol has a low toxicity and in dilute solutions is used as a mouth wash.

Chlorocresol.—Chlorocresol, *para*chloro*meta*cresol $CH_3.C_6H_3Cl.OH$.

CHARACTERS.—Colourless crystals; odour characteristic. *Solubility.* —1 in 250 of water, more in hot water, readily soluble in alcohol, ether and fixed oils.

ACTIONS AND USES

Chlorocresol is a bactericide—about ten times more efficient than phenol—and with relatively slight toxicity to the tissues. It is used (0·2 per cent.) to maintain the sterility of solutions or preparations, which have first been heated to 100° C. for 30 minutes (*see* p. 15) and is an official component of the Injections of Procaine and Adrenaline, Bismuthi and Bismuthi Oxychloridi.

Chlorocresol is more soluble in solutions of soap and may be used (1 per cent.) in soap solution as a general antiseptic; the soap solution, by lowering surface tension, not only cleanses the part but also aids the penetration of the bactericide.

Chloroxylenol.—*Para*chloro*meta*xylenol. 2-chloro-5-hydroxy-1 : 3-dimethyl-benzene. $(CH_3)_2.C_6H_2Cl.OH$.

CHARACTERS.—White crystals or powder, odour characteristic. Solubility, 1 in 3,000 of water, more in hot water, volatile in steam; soluble in alcohol, ether and solutions of alkali hydroxides.

Preparation

Liquor Chloroxylenolis.—Roxenol. Dettol. A yellow, soapy fluid. Chloroxylenol 5% and Terpineol 10% with Alcohol, Ricinoleic Acid, and Solution of Sodium Hydroxide in Distilled Water.

ACTIONS AND USES

Chloroxylenol is, when dissolved by alkalis or in soap solution, a potent antiseptic of low toxicity and not irritant. It is used as **Liquor Chloroxylenolis** which is diluted 1 in 10 or 20 of water as a general surgical and gynæcological antiseptic, and 1 in 200 as an oral antiseptic or gargle.

Acidum Ricinoleicum.—Ricinoleic Acid. A mixture of fatty acids obtained by hydrolysis of Castor Oil.

CHARACTERS.—A yellowish, viscous fluid with characteristic odour and taste; insoluble in water.

ACTIONS AND USES

Ricinoleic Acid, as its soluble soap, Sodium Ricinoleate, lowers surface tension and is an effective antiseptic and detergent. It is advised in 1 to 4 per cent. solutions as an oral antiseptic for gingivitis and pyorrhœa and may be used in tooth-pastes. Liquor Chloroxylenolis contains Ricinoleic Acid as its soap forms stable emulsions.

Terpineol.—Terpineol. $C_{10}H_{17}OH$. A mixture of isomers of which dl-α-terpineol predominates.

CHARACTERS.—A colourless, slightly viscous fluid; odour pleasant, taste bitter, slightly pungent; very slightly soluble in water.

ACTIONS AND USES

Terpineol is antiseptic and is used (10 per cent.) in Liquor Chloroxylenolis as a flavouring antiseptic.

Chloroazodin.—Azochloramid. Dichloroazodicarbamidine.

ACTIONS AND USES

Chloroazodin is an antiseptic, liberating chlorine slowly, and not toxic or impaired in action by serum or pus in wounds. A solution (1 in 3,300) in isotonc buffered saline solution is used in chest surgery for lavage and tuberculous empyemas, as well as for irrigation of abscesses, osteomyelitis and other infections. For septic wounds, burns, ulcers and abscess cavities, a 2 per cent. solution in glyceryl triacetate is soaked into gauze and applied to the infected area.

Creosotum.—Creosote. A mixture of Phenols, chiefly guaiacol and creosol, obtained by distillation of wood tar.

CHARACTERS.—A colourless or pale-yellow liquid; neutral or faintly acid; odour strong, empyreumatic; taste acrid. *Solubility.*—1 in 150 of cold, more so in hot, water; freely in alcohol 90%; in fixed and volatile oils.

COMPOSITION.—A variable mixture of *guaiacol*, $C_6H_4(OCH_3)OH$, *creosol*, $C_6H_4(OCH_3)_2$, and other phenols.

Dose.—Metric, 0·12 to 0·6 Mil; Imperial, 2 to 10 min.

ACTIONS AND USES

Externally.—Creosote is a **powerful antiseptic.** It produces on the skin a sensation of burning followed by numbness and local anæsthesia, and is sometimes used to relieve itching and irritation. An Ointment (10 per cent.) is applied in parasitic skin diseases, and in psoriasis and eczema.

Internally.—In the mouth Creosote is applied as an antiseptic and local anæsthetic (obtundent) to carious teeth. Given internally, a small amount is excreted in the lungs, where it is believed to exert an **antiseptic** action. It may reduce the amount and fetor of the sputum. It may be given orally in capsules, with Cod-liver Oil, or as an inhalation (1 in 250 of hot water), in phthisis, chronic bronchitis, gangrene and other pulmonary diseases. Combinations of Creosote, Iodine and other volatile antiseptics, such as Ether, Chloroform and Alcohol, are sometimes used as a "dry inhalation" in bronchial infections.

Resorcinol. Resorcin, *m*-dihydroxy-benzene. $C_6H_4(OH)_2$.

CHARACTERS.—Colourless, acicular crystals; odour faint; taste pungent, sweetish, later bitter. *Solubility.*—1 in 1 of water or alcohol; soluble in ether, glycerin and olive oil.

ACTIONS AND USES

Resorcin is **antiseptic, antipruritic and parasiticidal** without being irritant in 2 to 20 per cent. strengths. It is used as lotions, pastes (10 to 20 per cent.) with Zinc Oxide, Starch and Liquid Paraffin and as Ointments in treating chronic eczema, acne, psoriasis and other chronic and itching skin diseases. Hexylresorcinol is mentioned on p. 186.

Pyrogallol (B.P.C.).—Pyrogallic Acid. Trihydroxy-benzene. $C_6H_3(OH)_3$. White crystals. *Solubility.*—1 in 2 of water and in alcohol. Pyrogallic Acid is a reducing **antiseptic**. It is employed externally as an ointment (2 to 10%) for chronic skin diseases such as psoriasis, lupus, ringworm and chronic eczema.

Betanaphthol.—Beta-naphthol. β-hydroxynaphthalene. $C_{10}H_7OH$.

CHARACTERS.—White, crystalline lamellæ, or powder; odour like phenol; taste sharp, pungent. *Solubility.*—1 in 1,000 of cold, 1 in 75 of boiling, water, solutions neutral; 1 in less than 2 of alcohol 90%. **Dose.—Metric, 0·3 to 0·6 G; Imperial, 5 to 10 gr.**

ACTIONS AND USES

Betanaphthol is a powerful **antiseptic**, stronger than Phenol and less toxic. It is applied as a lotion or ointment (5 to 10 per cent.) in hyperidrosis, scabies, eczema and psoriasis. *Internally* it was prescribed as an **intestinal antiseptic** and as an **anthelmintic** in ankylostomiasis. It is excreted in combination with glycuronic acid, and turns the urine reddish.

Ichthammol.—Ichthyol. Ammonium Ichthosulphonate. The ammonium salts of the sulphonic acids of an oily substance, prepared from a bituminous schist, together with ammonium sulphate and water.

CHARACTERS.—A black viscid liquid; odour strong, characteristic. *Solubility.*—Soluble in water, glycerin and fats.

ACTIONS AND USES

Ichthyol is a moderate irritant and acts as a **stimulant antiseptic** in ointments and pastes (10 per cent.) for acne, eczema, favus and psoriasis. Gauze packs soaked in 2 to 5 per cent. solutions are used in cervicitis and leucorrhœa.

Pix Liquida.—Tar. Stockholm Tar. A bituminous liquid obtained by destructive distillation from the wood of various trees of the family Pinaceæ.

CHARACTERS.—Semi-liquid, dark brown; odour empyreumatic; reaction acid. *Solubility.*—1 in 10 of Alcohol 90%; in ether, chloroform, fixed and volatile oils.

COMPOSITION.—A variable mixture of *creosol, cresol, phenol, pyrocatechol, guaiacol, toluene, xylene, naphthalene* and *resinoids.*

ACTIONS AND USES

Tar is useful in ointments (10 to 70 per cent.) as a **stimulant antiseptic** in dry skin diseases, such as psoriasis, lichen planus, ichthyosis and certain forms of chronic eczema; and as a **sedative** in pruritus.

Pix Carbonis Præparata.—Prepared Coal Tar. Made by heating commercial Coal Tar in a shallow vessel at 50° C.

CHARACTERS.—A nearly black, viscous liquid; odour strongly empyreumatic. *Solubility.*—Very slightly in water; partially in alcohol 90% and in oils.

COMPOSITION.—A complex mixture of hydrocarbons: *benzene, toluene, naphthalene, anthracene, phenol compounds, aniline,* etc.

Preparation

Liquor Picis Carbonis.—Solution of Coal Tar. Prepared Coal Tar, 20%, emulsified by Quillaia in Alcohol 90%.

ACTIONS AND USES

Coal Tar is a **stimulating antiseptic** but too irritant for use in acute skin infections; it may be applied pure in chronic eczema but is usually employed as a 5 to 20 per cent. ointment or in alcoholic or oily lotions. Liquor Picis Carbonis is used in lotions, 5 to 10 per cent., for chronic eczema and psoriasis.

Oleum Cadinum.—Oil of Cade. Juniper Tar Oil. An oily liquid made by the destructive distillation of the woody portions of Juniperus Oxycedrus, N.O. Coniferæ.

CHARACTERS.—A dark reddish-brown, or nearly black, oily liquid; odour empyreumatic; taste acrid. *Solubility.*—Slightly in water; partly in cold, almost wholly in hot, alcohol 90%.

COMPOSITION.—A sesquiterpene, *cadinene,* $C_{15}H_{24}$.

ACTIONS AND USES

Oil of Cade is a **stimulant antiseptic** like Tar, applied (2 to 10 per cent.) with equal parts of soap and alcohol or as an ointment, in chronic eczema, psoriasis and other skin diseases, particularly if there is itching.

Balsamum Peruvianum.—Balsam of Peru. A Balsam exuded from the trunk of Myroxylon Pereiræ, N.O. Leguminosæ.

CHARACTERS.—A viscid, dark-brown liquid; odour agreeable, balsamic; taste acrid, bitter. *Solubility.*—Insoluble in water.

COMPOSITION.—Not less than 50% of balsamic esters, which are *benzyl benzoate*, $C_7H_7.C_6H_5.COO$, and *benzyl cinnamate*, $C_7H_7.C_8H_7$ COO; and about 28% of an alcoholic resin (*peru resinotannol*) united to *cinnamic* and *benzoic acids*; an aromatic alcohol (peruviol), *vanillin*, and *cinnamic acid.*

ACTIONS AND USES

Balsam of Peru is an **antiseptic** and **parasiticide.** It is used mainly in chronic inflammatory skin diseases, eczema, prurigo, urticaria, etc., to **relieve itching,** and in scabies because benzyl benzoate kills the acarus. The skin should be thoroughly rubbed with an ointment (60 gr. to 1 oz. of Soft Paraffin) on two or more occasions; a warm bath being taken before, and the application washed off in the morning with Soft Soap.

Styrax Præparatus.—Prepared Storax. A balsam obtained from the wounded trunk of Liquidambar orientalis, N.O. Hamamelideæ.

CHARACTERS.—A brown, viscid fluid; odour and taste, balsamic. *Solubility.*—Entirely in alcohol 90% and ether.

COMPOSITION.—Storax consists of not less than 30% of balsamic acids, chiefly *cinnamic acid*; a volatile oil, *styrol*, C_8H_8; *cinnamate of cinnamyl* (styracin) and a resin, *storesinol.*

ACTIONS AND USES

Storax is a **local stimulant, antiseptic and parasiticide.** It was used for scabies and pediculosis as an ointment (25 per cent.). It is contained in Tinctura Benzoini Composita.

Dithranol.—Dioxyanthranol. Cignolin. Anthralin. 1:8-dihydroxyanthranol. $C_{14}H_7(OH)_3$.

CHARACTERS.—An odourless yellow powder; insoluble in water, soluble in fixed oils.

Preparation

Unguentum Dithranolis.—Dithranol 0·1 per cent. in Yellow Soft Paraffin.

ACTIONS AND USES

Dithranol has displaced Chrysarobin for the treatment of psoriasis, lichen planus and chronic eczema; it is applied in 0·1 and up to 1 per cent. strengths as an ointment. It is a reducing antiseptic, and although it produces less discoloration of the skin and clothing and is less irritant than Chrysarobin, a small test application with it should be made first lest the patient is allergic to the drug.

PARASITICIDES

Benzylis Benzoas.—Benzyl Benzoate. $C_6H_5.CO_2.CH_2.C_6H_5$.

CHARACTERS.—Colourless crystals or oily liquid; odour faintly aromatic; taste sharp, burning. Insoluble in water and glycerin, soluble in alcohol (90%).

ACTIONS AND USES

Benzyl Benzoate is toxic to Acarus Scabiei and a speedy and cleanly method of treating scabies or itch is by the use of Applicatio Benzylis Benzoatis (B.P.C. and N.F.) which is Benzyl Benzoate 25, Emulsifying Wax 2 in Water to 100. The patient is first scrubbed in a hot bath with soft soap to open the burrows of the acarus and then painted with the Application by a brush over the whole body except the neck and head; when dry, a second application is made. One such treatment may suffice to eradicate the mite.

Benzyl Benzoate was formerly given internally (0·3–0·5 Mil) emulsified with Tragacanth, or as Benzyl Succinate (0·3 to 1 G) in tablets, as an antispasmodic for asthma, biliary, renal and intestinal colic, because it relaxed plain muscle.

Lauryl Thiocyanate.—Thiocyanates have proved valuable insecticides and a 25 per cent. solution of Lauryl Thiocyanate in Liquid Paraffin is an effective and non-irritating remedy for pediculus capitis. It is rubbed into the scalp once and left on for ten days; it destroys both lice and nits. Lethane 384 (Lethane Oil), β-butoxyl-β-thiocyanodiethylether, mixed with equal parts of White Mineral Oil, is Applicatio Lethani (N.F.), or Medicated (Lethane) Hair Oil, for the treatment of pediculus capitis.

Derris Præparata (B.P.C.).—Derris Powder, from the rhizome and roots of species of Derris or Lonchocarpus, contains from 4 to 6 per cent. of **Rotenone**. Derris was used in treating scabies as Derris 1, Hard Soap 1/4, Water 10; or as **Rotenone**, 1 or 2 per cent. lotions or ointments but it causes dermatitis in thin and moist areas of skin. It is also used as an insecticide and has a more rapid action than Dicophane.

INSECTICIDES AND REPELLANTS

These have become important medically for the control of insect vectors, such as mosquitoes in malaria and lice in communicating typhus fever.

Dicophanum (B.P.C.).—Dicophane. D.D.T. 2 : 2-di-(*p*-chlorophenyl)-1 : 1 : 1-trichloroethane.

CHARACTERS.—White crystals, powder or granules; almost insoluble in water, soluble in paraffin oil (1 in 20) and fixed oils (1 in 10).

ACTIONS AND USES

Dicophane acts slowly but for long periods as an insecticide and larvicide. Insects absorb the drug both orally and through the cuticle and it appears to act as a nerve poison. Owing to its slow action, it is commonly combined with Derris or Pyrethrum powder which have a rapid "knock-down" effect. It is used to control mosquitoes in malarial areas and as a 2 per cent. dusting powder, with French Chalk or Light Kaolin, blown between the skin and clothing to eradicate lice (especially in typhus outbreaks), fleas and bugs, or the clothing may be impregnated with it. For house flies, a spray of a 5 per cent. solution in paraffin oil will remain effective on walls for two to three months.

Applicatio Dicophani (B.P.C. and N.F.) contains 2 per cent. in Emulsifying Wax, Xylene, Citronella Oil and Water. About 1/2 fl. oz. is rubbed into the scalp and left on for 24 hours in the treatment of pediculus capitis.

While it is safe for use as described, workers with Dicophane should wear protective clothing as on absorption it acts as a peripheral nerve poison, causing muscular tremors and weakness and may cause liver necrosis.

Gammexane.—Benzene hexachloride. This is used as an insecticide mainly as a 5% dusting powder for rooms; its action is rapid and sustained.

Pyrethri Flos (B.P.C.).—The powdered dried flower heads of Chrysanthemum cinerariæfolium. Pyrethrum powder contains Pyrethrins, which are insecticides and repellants with a rapid but relatively brief action. The powder is used with French Chalk for clothing, and extracts in sprays for destruction of insect vectors. Pyrethrum and Derris may be mixed with Dicophane to afford by the former a rapid and by the latter a prolonged toxic efficiency.

Dimethylphthalate (B.P.C.).—This is an insect repellant and, as it is slowly volatile, it will on application to the skin or clothing repel fleas, midges, mosquitoes and other insect pests for about five hours. It may cause transient irritation of delicate skin. Lotions or creams containing 35 per cent. are usually employed.

Volatile Oils (e.g. Oil of Citronella) are not very effective as repellants.

COUNTER-IRRITANTS

Counter-irritants first stimulate and later paralyse sensory endings in the skin, and produce by an axon-reflex, and perhaps also by liberation of Histamine (*see* p. 381), local dilatation of superficial vessels together with local sensations of heat and pain which are followed by numbness. The superficial sensory irritation acts as a stimulus to the segment of cord with which the sensory neuron is connected, and hence there are produced reflexly vascular and trophic changes in deep-seated organs deriving their nerve supply from the same segment of the cord. Further, the sensory stimulus also influences the medullary centres from which reflexly impulses are sent out to quicken respiration and the heart and to raise blood-pressure. The relief of neuralgic and visceral pain by counter-irritants is psychic in origin, the common path for the transmission of pain being occupied by the new stimulus which engages the attention of the cerebral centres. There are three degrees of action—rubefacient, vesicant and pustulant.

Oleum Terebinthinæ.—Oil of Turpentine is distilled from the oleo-resin (turpentine) of various species of Pinus, N.O. Coniferæ, and rectified.

CHARACTERS.—A colourless liquid; odour characteristic; taste pungent. *Solubility.*—1 in 7 of alcohol 90%; in ether and chloroform. Mixes with other volatile and fixed oils, and dissolves resins.

COMPOSITION.—Oil of Turpentine, composed largely of *carene* or its isomers d- and l-pinene, $C_{10}H_{16}$, readily absorbs oxygen in sunlight from moist air and is converted into pinol hydrate, hydrogen peroxide, and camphoric acid.

Dose.—Metric, 0·2 to 0·6 Mil; Imperial, 3 to 10 min.

Preparation

Linimentum Terebinthinæ.—Turpentine, 65%, with Camphor, 5%, Soft Soap and Water.

ACTIONS AND USES

Externally.—Applied to the skin, Turpentine is, in emergency, an **antiseptic**, although somewhat irritant. When rubbed into the skin, it readily penetrates the epidermis, irritates the sensory endings, and produces redness from increased local circulation and a sense of warmth or heat; depression of the sensory endings follows and the area feels numb. Turpentine is therefore used as a **local rubefacient and counter-irritant** (*a*) to relieve pain and stiffness in muscles and joints from sprains, fibrositis, lumbago, and chronic rheumatism; (*b*) to produce, reflexly through the corresponding segment of the spinal cord, trophic and circulatory changes which modify inflammatory processes in deep-seated tissues for example to relieve pain and inflammation in pleurisy, bronchitis and pheumonia. For these purposes, Turpentine may be applied as the Liniment or, sprinkled upon cloths wrung out in hot water, i.e. as Turpentine "stupes," upon the area to which pain is referred.

Turpentine is also used by inhalation as a vapour from hot water as a bronchial antiseptic and expectorant.

Internally.—Turpentine acts like other Volatile Oils (p. 144). In the *mouth* it reflexly excites salivation, and in the *stomach* the movements are lessened and the muscle relaxed; thus it relieves colic and acts as a **carminative**, but is little used because of its taste. In the *intestine*, Turpentine is a carminative and relaxes the muscle, reducing flatulence, but in large doses it causes irritation and purgation. It is also an intestinal antiseptic, but rarely used as such. When added to purgative enemata, it relieves tympanites.

Turpentine is an **anthelmintic**, and is sometimes given either by the mouth for removal of tapeworm, in doses of 2 to 4 fl. dr., which sometimes cause severe diarrhœa, or as an enema (1 to 4 fl. dr. with 1 oz. soft soap in 1 pint water) for threadworm.

Actions after absorption.—Oil of Turpentine is absorbed from the intestine. Large doses cause gastro-enteritis and, upon absorption, produce, after a stage of cortical stimulation and motor excitement, depression of the cerebrum, medulla and cord with symptoms of lethargy, unsteady or inco-ordinate movements, diminished reflexes and finally coma.

Excretion.—Oil of Turpentine, like Volatile Oils, is excreted mainly as such through the lungs and bronchial mucous membranes, by the kidneys, and to a slight extent by the skin. It acts as a stimulant to the bronchial mucous glands and is a mild pulmonary antiseptic although unpleasant to take.

Its renal excretion produces, by irritating the renal epithelium, **diuresis**, and in the urine it acts as an antiseptic. Even moderate doses may cause lumbar or perineal pain, difficulty in micturition and albuminuria or hæmaturia; therefore it is seldom used. Part is excreted as a fragrant body which imparts to the urine the odour of violets.

Colophonium.—Colophony. Resin. The residue left after distillation of Oil of Turpentine from the oleo-resin of various species of Pinus, N.O. Coniferæ.

CHARACTERS.—Translucent, light amber, brittle masses. *Solubility.*—Insoluble in water, soluble in alcohol 90%, and ether.

COMPOSITION.—Resin contains three isomeric *abietic acids*, α, β and γ, $C_{19}H_{28}O_2$; traces of volatile oil; and *resene*.

ACTIONS AND USES

Resin is an **adhesive**, and is a common basis for plasters and adhesive strapping; it is contained in Flexible Collodion. As adhesives, rubber plasters are better. It is a **stimulant** for skin diseases in the form of an ointment (20 per cent.).

Oleum Eucalypti.—Oil of Eucalyptus. The oil distilled from fresh leaves of Eucalyptus, N.O. Myrtaceæ, and rectified.

CHARACTERS.—Pale yellow; odour aromatic, camphoraceous; taste pungent, leaving a sensation of cold.
COMPOSITION.—Not less than 70% of *cineole* (eucalyptol); *d-pinene*, $C_{10}H_{16}$ and other terpenes; alcohols, aldehydes, and phellandrene.
Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

Eucalyptol.—Eucalyptol. Cineole. $C_{10}H_{18}O$. The anhydride of menthan-1 : 8-diol obtained from Oil of Eucalyptus.

CHARACTERS.—A colourless liquid; odour aromatic; taste pungent, cooling. *Soluble* in fats and paraffin.
Dose.—Metric, 0·06 to 0·2 Mil; Imperial, 1 to 3 min.

ACTIONS AND USES

Externally.—Eucalyptus Oil and Eucalyptol are stimulating **antiseptics** used in ointments (10 per cent.) for minor skin infections, and also **rubefacient** counter-irritants (50 per cent. in Olive Oil). The inhaled vapour, and sprays, containing 5 min. in 1 fl. oz. of Liquid Paraffin along with equal strengths of Methyl Salicylate and Menthol, are frequently used as prophylactics and antiseptics for nasal catarrhs and influenza. Inhalation of the vapour from hot water (3 to 5 min. in a pint) is used in treating bronchial catarrhs, etc.

Internally.—The oil is a popular remedy on sugar for colds; narcosis occurs from overdose.

Camphora.—Camphor. $C_{10}H_{16}O$. A ketone obtained from Cinnamomum Camphora, N.O. Lauraceæ; or synthetically from pinene in Turpentine by conversion into camphene and by oxidation.

CHARACTERS.—Colourless crystals, rectangular tablets or powdery masses known as "flowers of camphor." Odour characteristic, taste pungent, followed by sensation of cold. Sublimes without residue. *Solubility.*—1 in about 700 of water; 1 in about 1 of alcohol 90%; 1 in 4 of olive oil. Forms a liquid if rubbed with Chloral Hydrate, Menthol, Phenol or Thymol.
Dose.—Metric, 0·12 to 0·3 G; Imperial, 2 to 5 gr.

Preparations

1. **Aqua Camphoræ.**—Camphor, 0·1%, with Alcohol 90% in Water.
Dose.—Metric, 15 to 30 Mils; Imperial, 1/2 to 1 fl. oz.

2. **Linimentum Camphoræ.**—"Camphorated Oil." Camphor, 20% in Olive Oil.
3. **Linimentum Camphoræ Ammoniatum.**—Camphor 12·5%, with Oil of Lavender, Strong Solution of Ammonia, and Alcohol 90%.
4. **Spiritus Camphoræ.**—Camphor, 10% in Alcohol 90%.
Dose.—Metric, 0·3 to 2 Mils; Imperial, 5 to 30 min.
5. **Tinctura Opii Camphorata.**—Tinctura Camphoræ Composita. Paregoric. Camphor, 0·3%, Tincture of Opium, 5% with Benzoic Acid and Oil of Anise in Alcohol 60%. 4 Mils (60 min.) contain 2 mg (1/30 gr.) Morphine.
Dose.—Metric, 2 to 4 Mils; Imperial, 30 to 60 min.

ACTIONS AND USES

Externally.—Camphor, when rubbed into the skin, is (1) a weak **antiseptic**; (2) a **rubefacient** by first irritating the sensory endings; (3) a **local anodyne** by later paralysing the sensory endings. The external uses of the many liniments and ointments containing Camphor depend on these actions; they are used as **counter-irritants** for sprains, synovitis, muscular rheumatism, lumbago, neuralgias, etc., and for inflammatory conditions of the throat, bronchioles and lungs. The presence of Camphor in Injectio Bismuthi Salicylatis is designed to allay pain and, by increasing the circulation in the part, to promote absorption.

Internally.—The liquid mixtures which Camphor forms with Phenol and Chloral form antiseptic obtundent dressings for carious teeth. Camphor 1 with Precipitated Chalk 7 is an inexpensive **dentifrice**; it increases the buccal circulation and salivation.

In the *stomach*, Camphor is a weak **antiseptic** and a moderate **irritant**; it gives rise to a sensation of warmth and some nausea together with relaxation of any spasmodic contraction of the muscle. The irritation and nausea produce reflexly through the vagus increased secretion of bronchial mucus and, therefore, Camphor is a valuable **expectorant**. It is used to increase and liquefy the bronchial secretions chiefly in the form of the Tinctura Opii Camphorata, in which the Benzoic Acid and Oil of Anise also are expectorants, while the Opium prevents sickness, diminishes painful cough and promotes sleep. This tincture is prescribed in many mixtures for the treatment of cough in bronchial catarrhs, broncho-pneumonias and in the resolution stage of pneumonia, etc. In common colds, it often reflexly induces perspiration and thus acts as an **antipyretic** also. Aqua Camphoræ is a common flavour for expectorant mixtures.

Spiritus Camphoræ, owing to the gastric irritation of the Camphor and Alcohol, is useful as a **reflex restorative** or "diffusible stimulant" in fainting or circulatory collapse and in hysteria. It is also useful by relaxing muscular spasm as a **carminative** in gastric, and to a lesser extent in intestinal, flatulence.

Effects after absorption.—Camphor is absorbed slowly from the skin but readily from the intestine. It has no therapeutic value in the tissues. Toxic doses produce at first stimulation of the cerebral cortex, resulting in excitement, confusion and headache, with occasional delirium and hallucinations.

Excretion.—Camphor is rapidly oxidized into camphorol, $C_{10}H_{15}O.OH$, which, combined with glycuronic acid, is excreted by the kidney. It does not have any diuretic or antiseptic value during excretion.

Menthol.—Menthol. $C_6H_9.CH_3.OH.CH(CH_3)_2$. Menthol is lævo-menthol, natural or synthetic, or racemic menthol.

CHARACTERS.—Colourless acicular crystals; odour and taste of peppermint; on the tongue, causes sensation of warmth followed by coolness. *Solubility.*—Sparingly in water; readily in oils, and liquid paraffin.

ACTIONS AND USES

Externally.—Menthol, rubbed upon the skin, causes some smarting and a sensation of coolness; this is due to stimulation (increased excitability) of both sensory and temperature receptors. The sensory irritation results in a mild **rubefacient** effect and, when sensory paralysis follows, **numbness** of the area results. Menthol cones, ointments (15 per cent.) and liniments (10 to 20 per cent.) with Chloroform and Olive Oil are rubbed over neuralgic areas as **local anodynes** to relieve pain in lumbago, sciatica, pruritus and chronic rheumatism. Menthol is also **antiseptic**, and sprays (0·5 to 2 per cent.) in Liquid Paraffin are useful in naso-pharyngeal catarrhs, or as drops to relieve earache; pastilles containing 1/20 gr. are used for laryngitis, and mixtures with Phenol and Camphor are used as antiseptic anodynes in dentistry.

Sinapis (*not official*).—Mustard. The powdered ripe seeds of Brassica alba, White Mustard, and Brassica sinapoides, Black Mustard, N.O. Cruciferæ.

CHARACTERS.—A yellow, odourless powder; when moist, odour pungent; taste, very pungent.

COMPOSITION.—White Mustard Seeds contain a glycoside *sinalbin* which by an enzyme *myrosin* is hydrolysed in water to form acrinyl isothiocyanate, sinapine acid sulphate and glucose; also 30% of fixed oil. Black Mustard Seeds contain a glycoside *sinigrin* (potassium myronate) which with *myrosin* forms allyl isothiocyanate

(Volatile Oil of Mustard), potassium acid sulphate and glucose; also 27% of fixed oil. Both acrinyl and allyl isothiocyanates are powerful irritants.

ACTIONS AND USES

Externally.—When applied to the skin, Mustard produces rapidly: (1) Sensory **irritation** and a **rubefacient** action resulting in redness, heat and severe burning pain; (2) **diminished sensation** in the area later from paralysis of the sensory endings; (3) **vesication**, if the application be prolonged, because of the exudation of lymph from the capillaries. The deeper tissues and viscera, which derive their nervous supply from the same segment of the cord as the affected area, may reflexly have their blood supply modified. The heart, blood-pressure, respiration and nervous centres generally are reflexly stimulated by the application of Mustard to the skin.

In the form of a poultice (Mustard 2, Linseed 28, Water 100) or a Mustard plaster, Mustard is extensively used as a readily available and rapid means of producing **counter-irritation.** Mustard poultices are applied to relieve the pain of neuralgia and muscular rheumatism (lumbago, etc.) and also of laryngitis, and pleurisy. They should be applied over the cutaneous area to which the visceral pain is referred. As a reflex cardio-vascular and respiratory stimulant, a Mustard plaster (or sinapism) may be applied to the calves or soles in syncope, coma or asphyxia. Diffused through a warm bath (1: 500, or a dessertspoonful per gallon), it is a popular means of dilating superficial vessels at the onset of "colds" and febrile diseases, as well as in infantile convulsions.

Internally.—Mustard produces a pungent impression on the tongue and olfactory organs, a sense of warmth in the stomach, with increase of relish and appetite and of the circulation in the gastric wall. Mustard is therefore the most familiar of condiments. In full doses it is a rapid stimulant **emetic**, which causes little subsequent depression. From one to four teaspoonfuls of powdered Mustard may be given, stirred up with a tumblerful of warm water, in cases where other emetics are not available or have failed, especially in poisoning by narcotics.

Capsicum.—Capsicum. The dried ripe fruit of Capsicum minimum, N.O. Solanaceæ.

CHARACTERS.—Dull orange-red fruits; pericarp shrivelled; seeds small and flat. Odour characteristic; taste very pungent.

COMPOSITION.—Capsicum yields a crystalline, pungent body; *capsaicin*, $C_{18}H_{27}O_3N$; a liquid alkaloid; a red colouring matter; and *fixed oil.*

Preparations

1. **Tinctura Capsici.**—Capsicum, 5% in Alcohol 60%.
Dose.—Metric, 0·3 to 1 Mil; Imperial, 5 to 15 min.
2. **Unguentum Capsici.**—Capsicum, 25%, in Lard, Hard and Yellow Soft Paraffins.

ACTIONS AND USES

Externally.—Capsicum (*capsaicin*) is a powerful sensory **irritant** and **rubefacient**; the Ointment, a Plaster or "Capsicum Wool" may be applied as a **stimulant** and **counter-irritant** for rheumatism, lumbago and neuralgia.

Internally, it is used as a **condiment** (Cayenne pepper); and the Tincture is given medicinally as a **pungent, stomachic carminative and stimulant** to dispel flatulence and rouse the appetite, especially in alcoholic subjects.

Aconitum.—Aconite Root. The dried root of Aconitum Napellus, Monkshood, N.O. Ranunculaceæ.

CHARACTERS.—A conical, dark-brown root, crowned with base of stem; internally, starchy. Taste slight, followed by sensation of tingling and numbness.

COMPOSITION.—The alkaloid *aconitine*, $C_{34}H_{45}NO_{11}$. *Benzaconine* (*picraconitine*), $C_{32}H_{45}NO_{10}$, *aconine*, $C_{25}H_{41}NO_9$, and other more or less allied alkaloids, occur along with it. They are combined with an acid, *aconitic acid*, $C_3H_3(COOH)_3$. Contains about 0·5% of alkaloids.

Preparation

Linimentum Aconiti.—Aconite Root 50, with Camphor 3% in Alcohol 90%.

ACTIONS AND USES

Externally.—If Aconitine be applied to the skin in the form of an ointment (2 per cent.) or to a mucous membrane as a dilute solution, it produces a sensation of tingling and warmth by stimulation of sensory nerve endings; depression then sets in, resulting in numbness and loss of sensation. Aconite Liniment is used to relieve the pains of acute and chronic rheumatism, neuralgia and myalgia. It should be applied with great care, particularly near the eye.

Internally.—A Tincture of Aconite (2 to 5 min.) or solution of Aconitine (1 : 10,000) causes tingling and anæsthesia of the buccal mucous membrane; in the stomach, large doses produce a feeling of warmth and pain preceding sickness. Easily absorbed, Aconitine causes first a stimulation of the vagus centre, hence the cardiac beats are slower and weaker and blood-pressure falls. Larger doses stimulate the rhythmogenic area and the muscle directly, so that the cardiac rate and force and the blood-pressure again increase. Finally depression of A-V conductivity occurs, producing heart-block and arrhythmia.

In man, therapeutic doses merely slow and weaken the pulse. Since it dilates the cutaneous vessels and promotes sweating, Tincture of Aconite was formerly used to **lower febrile temperature**, particularly in children, but it is an unreliable antipyretic.

Oleum Hydnocarpi.—Hydnocarpus Oil. The fatty oil obtained by cold expression from the fresh, ripe seeds of Hydnocarpus Wightiana, N.O. Pangiaceæ.

CHARACTERS.—A yellowish oil; odour slight, taste acrid. *Solubility.*—Insoluble in water and cold alcohol.

COMPOSITION.—Glycerides of *hydnocarpic* and *chaulmoogric acids.*

Dose.—*Orally:* **Metric, 0·3 to 1 Mil, increasing to 4 Mils.**
Imperial, 5 to 15 min., increasing to 60 min.

Preparation

Injectio Olei Hydnocarpi.—Hydnocarpus Oil sterilized by heating at 150° C. for 1 hour.

Dose.—*By subcutaneous or intramuscular injection:*
Metric, 2 Mils, increasing to 5 Mils.
Imperial, 30 min., increasing to 75 min.

Oleum Hydnocarpi Æthylicum.—Ethyl Esters of Hydnocarpus Oil. The ethyl esters of chaulmoogric and hydnocarpic acids.

CHARACTERS.—A faintly yellow, limpid oil; odour characteristic; taste acrid.

Dose.—*Orally:* **Metric, 0·3 to 1 Mil, increasing to 4 Mils.**
Imperial, 5 to 15 min., increasing to 60 min.

Preparation

Injectio Olei Hydnocarpi Æthylici.—Ethyl Esters of Hydnocarpus Oil sterilized by heating at 150° C. for 1 hour.

Dose.—*By subcutaneous or intramuscular injection:*
Metric, 2 Mils, increasing to 5 Mils.
Imperial, 30 min., increasing to 75 min.

ACTIONS AND USES

Oleum Hydnocarpi and its Ethyl Ester are irritant, and when given by mouth, the dosage must be increased gradually in order to avoid nausea, vomiting and purging. They are efficient remedies in **leprosy**, especially in early cases (under five years' duration), and are given orally in capsules or emulsified with Acacia and flavoured with Cinnamon; or injected deeply in the gluteal muscles twice weekly for months. The drugs cause degeneration and disappearance of the bacilli from the lesions, arrest the disease and cause retrogression of the nodules, anæsthetic areas and other skin conditions. To minimize the irritation of intramuscular injections, the oil may be diluted with Olive Oil, and 4 per cent. of Creosote or Camphor added as an anodyne. Intradermal injections in affected areas of skin are also advised. The action is thought to be due to a specific toxicity of these cyclic fatty acids for acid-fast bacteria, but the tubercle bacillus is not influenced. Injections are more effective than oral dosage, as absorption from the intestine is inconstant.

Oleum Chaulmoogræ and Sodium and Ethyl Chaulmoogrates are used similarly (*see* Sulphones, p. 410).

SCLEROSING AGENTS FOR VARICOSE VEINS

Æthanolamina.—Ethanolamine.-β-aminoethanol. $NH_2.CH_2.CH_2.OH$.

CHARACTERS.—A colourless or pale-yellow liquid, odourless; soluble in water.

Preparation

Injectio Æthanolaminæ Oleatis.—Ethanolamine 0·91% with Oleic Acid, Benzyl Alcohol in Water for Injection.

Dose.—*By intravenous injection as a sclerosing agent:*
Metric, 2 to 5 Mils; Imperial, 30 to 75 min.

ACTIONS AND USES

Ethanolamine Oleate Injection is used to sclerose varicose veins, it is less liable to cause sloughing than other agents, if any escapes outside the vein. Injections are made of 1/2 to 1 Mil at different levels of the vein, and repeated, if necessary, after a week's interval.

Injectio Quininæ et Urethani.—Quinine Hydrochloride 12·5, Urethane 6·25 in Water for Injection to 100.

Dose.—*By intravenous injection as a sclerosing agent:*
Metric, 0·5 to 5 Mils; Imperial, 8 to 75 min.

ACTIONS AND USES

Quinine and Urethane Injection may deposit solid matter on standing; this should be redissolved by warming and the syringe should be warmed before injecting the fluid, which is given in divided amounts into different parts of the vein.

DIAGNOSTIC DYES

Fluoresceinum Sodium.—Soluble Fluorescein. $C_{20}H_{10}O_5Na_2$. The disodium salt of Fluorescein.

CHARACTERS.—An orange-red powder; odourless; almost tasteless. *Solubility.*—1 in 1 of water.

ACTIONS AND USES

Externally.—A solution of Fluorescein 2 per cent. with Sodium Bicarbonate 3 per cent. in sterile water is dropped upon the conjunctiva in order to show up lacerations or ulceration upon the cornea; lesions of the epithelium are stained green, the colour lasting for some hours.

Methylthioninæ Chloridum.—Methylene Blue. Tetramethylthionine Chloride. $C_{16}H_{18}N_3ClS,3H_2O$.

CHARACTERS.—A dark-greenish, crystalline powder with metallic lustre; odourless. *Soluble* in water, and alcohol 90%.
Dose.—Metric, 60 to 300 mg; Imperial, 1 to 5 gr.

ACTIONS AND USES

Methylene Blue is an **antiseptic**, weak but not irritant, used in 0·25 to 2 per cent. lotions on mucous membranes, e.g. bladder, colon. It has been given orally as a urinary antiseptic.

It is mainly used as a test for renal function; when 1 Mil of a 5 per cent. solution is injected intramuscularly or hypodermically, the urine becomes green in 15 to 30 minutes and the colour deepens up to 4 hours.

VACCINE AND SERUM THERAPY

Vaccine therapy consists in the inoculation of an individual with the attenuated or killed virus of a disease, in order to produce a condition of resistance or immunity to that disease. Thus the use of vaccines may be either prophylactic or remedial. There are two forms of artificial immunity. The first, *active immunity*, is the condition of active resistance produced by a series of inoculations of non-lethal doses of an organism or its toxins—that is to say, either with the attenuated living organism, or the dead organism, or with the toxin obtained by filtering cultures of the organism. The second form, *passive immunity*, is conferred by the injection of antitoxic sera obtained from an animal actively immunized against a particular toxin or bacterium. The first, active immunity, is much the more powerful; but serum therapy, or the use of antisera, is essential for treating acute diseases.

Preparation of Vaccines.—Vaccines containing *attenuated* organisms may be obtained (i) by cultivating the organism on culture media, (ii) by passing the organism through another species of animal, (iii) by cultivation at a higher temperature, or (iv) by treating the organism with weak antiseptic media. The virulence of the organism can thus be diminished, and the resulting attenuated form may be employed for the production of active immunity by inoculation, e.g. smallpox vaccine. The attainment of active immunity by the injection of subtoxic doses of virulent organisms is too dangerous to use in practical therapeutics.

Active immunity is also stimulated by the injection of cultures containing *dead* organisms. This is most frequently employed therapeutically, and such vaccines are prepared as follows: (1) The causal organism is obtained from the seat of the lesion, and isolated in pure culture at 37° C. on a suitable medium. (2) The culture growth is emulsified in about 5 c.c. of a 0·9 per cent. NaCl solution. (3) The bacterial emulsion is transferred to an incubator, and sterilized by heating at 60° C. for from 30 to 50 minutes or under appropriate conditions for each organism. (4) The number of bacteria in the emulsion is estimated: (*a*) by counting the bacteria with an ordinary hæmocytometer or (*b*) by opacity tests. (5) The emulsion is diluted with Normal Saline Solution until each c.c. contains an appropriate number of organisms, e.g. 10 millions, for a dose. (6) The sterility of the emulsion is proved, and a small amount of antiseptic, e.g. Phenol 0·5 per cent., or Tricresol 0·25 per cent., is added, and the vaccine is filled into sterile glass phials for use. The phial is opened, the contents are transferred to a sterile syringe, and the vaccine is injected subcutaneously or intramuscularly under aseptic precautions.

Actions of Vaccines.—The actions are seen (1) in the *blood*, (2) *locally*, and (3) in the *general* condition of the patient.

(1) When a person is injected with a medium dose of a vaccine there occurs, first, a reduction in the number of bacteria that the polymorphonuclear leucocytes (phagocytes) ingest and destroy—the *negative phase*; and the patient's resistance to the disease is probably lowered. The negative phase is succeeded in three or four days by a *positive phase* when resistance is increased. The vaccine (antigen) has stimulated the formation of antibodies, e.g. *opsonins* which lower bacterial resistance to the leucocytes, *bacteriolysins* which along with "complement" from the serum dissolve bacteria, *bactericidins* which kill without lysis, and *agglutinins* which clump germs. Reaching a maximum, antibody formation remains constant for some days, and then commences to fall. If a second injection be given during the negative phase, a greater and undesirable fall in the antibacterial activity of the blood occurs; but if the second injection be timed so as to arrive during the positive phase, a brief negative phase is followed by a

greater positive phase. Doses of vaccines are therefore repeated every 7 to 10 days. A large initial dose causes a decided negative phase, and therefore is not advisedly repeated for 10 days.

(2) *Local reactions.*—After the injection of a vaccine, there may occur in about 4 to 8 hours slight swelling and redness of the injected part, with tenderness and perhaps stiffness of the limb on movement. The reaction subsides in 24 to 48 hours.

(3) *General reactions.*—If the vaccine is employed prophylactically, in which case a large dose is usually given, there occur, within a few hours, headache, lassitude, pains in the limbs, and other febrile symptoms, accompanied by a rise in temperature to 100° or 102° F.; these symptoms subside in from 12 to 24 hours. If the vaccine is used in small initial dosage as a curative agent, little disturbance is observed; within the first day there may be slight malaise, irritability or drowsiness. After the initial dose no further ill-effects are observed—rather there is an improvement in appetite and general bodily vigour; and the fever and other symptoms of the disease improve.

Autogenous and Stock Vaccines.—An *autogenous vaccine* is one prepared directly from the patient, and is preferable. A *stock vaccine*, one prepared from a similar case, is commonly used and is satisfactory. Stock vaccines are usually *polyvalent*, that is, a mixture of different strains, ready for use in cases where the nature of the infection is unknown.

Vaccina Bacteralia.—Bacterial Vaccines. A bacterial vaccine is either a sterile suspension of micro-organisms or a sterile extract or derivative of micro-organisms; they may be simple or compound.

CHARACTERS.—Liquid suspensions of varying opacity, usually white; they should be stored at temperatures between 0° and 20° C.

Vaccinum Acnes.—Acne Vaccine. 1 Mil contains 20, 100 or 1,000 million Corynebacterium acnes.

Dose.—*Therapeutic:* 5 million (initial) increasing to 1,000 million; repeated in 3 to 10 days.

USES

It is used with benefit in early cases of acne, where the comedones are filled with caseous sebum, and suppuration has not occurred; in pustular acne, staphylococcic vaccine may also be given.

Vaccinum Choleraicum.—Cholera Vaccine. 1 Mil contains 8,000 million Vibrio choleræ.

Dose.—*Prophylactic:* first dose, 0·5 Mil; second dose, after an interval of 7 to 14 days, 1 Mil.

USES

It is effective as a prophylactic but not in treatment.

Vaccinum Dysentericum (Flexner).—Dysentery Vaccine (Flexner). 1 Mil contains 100 million each of the V. W. X. Y. Z. types of B. flexneri.

Dose.—*Prophylactic:* first dose, 0·5 Mil; second dose, after 7 to 14 days, 1 Mil; third dose, after 7 to 14 days, 1 Mil.

USES

This is now rarely used for prophylactic purposes.

Vaccinum Pertussis.—Whooping-Cough Vaccine. 1 Mil contains 1,000 to 10,000 million Hæmophilus pertussis in Phase I.

Dose.—*Prophylactic:* 1,000 to 20,000 million on 4 to 5 occasions at intervals of 1 to 7 days.

Therapeutic: 500 to 10,000 million at intervals of 1 to 7 days.

USES

As a prophylactic given usually about the age of three months, it may lower the liability to infection and reduce the severity of the disease: the protection lasts about three years. Therapeutically, it is not advantageous.

Vaccinum Pestis.—Plague Vaccine. 1 Mil contains 2,000 million Pasteurella pestis.

Dose.—0·5 to 1 Mil.

USES

Two doses of 0·5 and 1 Mil are usually given at 10 days' interval. It is not an absolute protective, but diminishes the risk and lowers the death rate. The immunity is short and reinoculation is desirable every six months; local and general reactions are common, lasting two days.

Vaccinum Staphylococcicum.—Staphylococcus Vaccine. 1 Mil contains 100 to 1,000 million Staphylococcus aureus.

Dose.—*Therapeutic:* 10 to 1,000 million at intervals of 3 to 7 days.

USES

This, combined with local treatment, was formerly used for boils and carbuncles, but it has been displaced by Penicillin, Sulphonamides and by Staphylococcus Toxoid.

Vaccinum Typho-paratyphosum.—Antityphoid-paratyphoid Vaccine. T.A.B. Vaccine. A sterile suspension containing in 1 Mil 1,000 million B. typhosus (Salmonella typhi); and 500 million each of B. paratyphosus (S. paratyphi) A and B, with an antiseptic equivalent to 0·5% phenol; sealed in glass ampoules.

CHARACTERS.—A colourless, opalescent liquid.

Dose.—*By cutaneous injection:*

First dose, 0·25 to 0·5 Mil; second dose after 7 to 21 days' interval, 0·5 to 1·0 Mil.

USES

T.A.B. vaccine is a **valuable prophylactic** against infection from all three forms of typhoid fever, and should be given to all persons a fortnight before entering regions where typhoid is prevalent or sanitary conditions primitive. Vaccination diminishes susceptibility to infection and lowers the mortality rate if the disease be acquired. The large doses required to induce immunity usually cause some febrile and local reactions, but they are rarely severe. Immunity lasts about a year.

Vaccinum Typhi Exanthematici.—Typhus Vaccine. A sterile suspension of typhus Rickettsiæ which have been killed; it is prepared from Rickettsiæ-infected yolk-sac of fertile eggs, lungs of small rodents or peritoneal cavities of gerbils.

CHARACTERS.—A slightly turbid liquid; the Rickettsiæ deposit on standing and are redistributed by shaking; stored in the dark at 4° C., it remains potent for one year.

Dose.—*By subcutaneous injection:*

0·25 to 1 Mil (4 to 15 min.).

USES

Three doses of 1 Mil are given at intervals of 7 to 10 days, then 1 Mil every six months. It is to some extent prophylactic against infection, mitigates the disease, and lowers the death rate.

Vaccinum Febris Flavæ.—Yellow Fever Vaccine. A serum-free aqueous suspension of chick embryo tissue infected with a strain of yellow fever virus known as 17 D which, although toxic to mice, is avirulent to man, but is an efficient antigen.

CHARACTERS.—It is supplied as a dry sterile powder, readily soluble in water or saline; labelled with the quantity of vaccine which contains 500 LD 50 doses. (The LD 50 dose is the quantity which causes death of 50 per cent. of mice within 21 days after intracerebral injection.)

Dose.—*By subcutaneous injection:* Not less than 500 LD 50 doses.

USES

Yellow fever vaccine gives in about 10 days an active immunity which lasts for 2 to 4 years, when reinoculation is desirable. The solid product is dissolved for use in cold Water for Injection or Injection of Sodium Chloride.

Vaccinum Tuberculinum.—Tubercle Vaccine. New Tuberculin, 1 Mil contains 0·00001 to 0·1 mg of Mycobacterium tuberculosis.

Dose.—*Therapeutic:* 0·000001 to 0·1 mg at intervals of 3 to 7 days.

USES

This is practically never given therapeutically.

Tuberculinum Pristinum.—Old Tuberculin. The concentrated filtrate from a fluid medium containing 5% of Glycerin on which Mycobacterium tuberculosis has grown for six or more weeks.

CHARACTERS.—A transparent, yellow or brown, viscous liquid; odour of honey. Old Tuberculin T. is prepared from the human type of bacilli and Old Tuberculin P.T. from the bovine type.

ASSAY.—By comparing in guinea-pigs, sensitized three weeks previously by intramuscular injection of B. tuberculosis, the inflammatory reaction produced after 24 hours by a hypodermic injection with that produced by an equivalent dose of the standard preparation.

Dose.—*Diagnostic, by intradermal injection:*

Metric, 0·00001 to 0·001 Mil; Imperial, 1/6,000 to 1/60 min.

USES

Tuberculin is used in the diagnosis of tuberculosis.

Intradermal Test (Mantoux).—Inject 0·1 Mil of a 1: 10,000 dilution of Tuberculin in Normal Saline intradermally: 24 to 48 hours later a red flush 1 cm. or more in diameter with central thickening is a positive reaction. This is presumptive of active tuberculous disease in children under 5, probably diagnostic in older children if they are not in health; in adults a positive reaction is less indicative of active lesions but a negative reaction usually excludes tuberculosis. If a final test with 0·1 Mil of a 1: 100 dilution produces no reaction, the patient is "Mantoux negative."

Scarification Test (Von Pirquet).—Through a minute drop of Tuberculin on the skin, a small surface scratch is made: 24 to 48 hours later a papular swelling and hyperæmia about 1 cm. in diameter is a positive reaction.

Patch Test (Vollmer).—This uses a strip of adhesive plaster on which are applied three squares of filter paper, the outer two impregnated with Old Tuberculin, or the protein derivative, the middle (control) with glycerin broth. It is applied to the skin, cleansed with ether, in the sternal or scapular area for 48 hours, then removed and the effect decided after another 24 hours; in a positive reaction, the outer squares are red and indurated with small vesicles.

Tuberculini Derivativum Proteinicum Purificatum.—Purified Protein Derivative of Tuberculin. Tuberculin P.P.D. This is the protein active principle of Old Tuberculin and is made by fractional precipitation of a fluid medium on which Mycobacterium tuberculosis has been grown.

CHARACTERS.—A dry cream-coloured powder or brown liquid. Caution: the powder, if inhaled, may cause toxic effects.
Dose.—*Diagnostic, by intradermal injection:* 0·1 Mil of solutions containing in each Mil the equivalent in potency to 0·0001 Mil, 0·001 Mil, or 0·01 Mil of the standard preparation of Old Tuberculin.

USES

In the diagnosis of tuberculosis by the Mantoux skin or Vollmer's patch test.

Vaccinum Vacciniæ.—Vaccine Lymph. The lymph from vesicles caused by inoculation of vaccinia virus on the skin of healthy animals is treated with glycerin to reduce the living organism to not more than 20,000 per Mil; sealed in sterile glass capillary tubes holding usually one human dose.

CHARACTERS.—A viscid, colourless fluid, containing white suspended matter. Store below 0° C.; above 10° C. potency may be lost in 7 days.
Dose.—*By scarification:*
Metric, 0·06 Mil; Imperial, 1 Min.

USES

Vaccination lymph is an effective *prophylactic against smallpox*; it has eradicated the disease from this country. Immunity lasts about 7 years, after which revaccination is advisable if entrance to an infected area be intended. Vaccination is best done in infancy by multiple pressure, scarification or intradermal injection. There is abundant proof of its protective value against smallpox and, even if infection be acquired, the disease in vaccinated persons runs a benign course and scarring from pustulation is averted.

ANTITOXIN OR SERUM THERAPY

Serum-therapy consists in the use of serum derived from the blood of an animal which has been immunized to a microbic disease by injections either of the organism or of the toxins produced by the organism. The principle is based on the theory of *passive immunity*, which may be stated shortly thus: When an animal is injected repeatedly with small and increasing doses of a pathogenic organism or its toxin, there develop in its serum antitoxic globulins which have the power of antagonizing the organisms or neutralizing the toxin: this is *active immunity* such as is procured by vaccine therapy and by the injection of Diphtheria

Prophylactic. If the serum of the actively immune animal be injected into a second animal, or into man, it confers on him an immunity, usually temporary, to that particular bacillary toxin: this is *passive immunity*. This treatment is *preventive* if the antiserum be introduced immediately prior to infection or shortly after its occurrence; and also *curative* if it be injected soon after the disease becomes manifest. An **antitoxin** is serum, or a preparation of serum, containing the antitoxic globulins or their derivatives, which have the specific power of neutralizing the toxins formed by a micro-organism.

Preparation.—Sera are made by injecting into a horse in graded doses the organismal toxins, until the animal is capable of tolerating many thousands times the fatal dose. A portion of the animal's blood is allowed to flow into sterile vessels, the blood defibrinated, the serum removed and filtered, and a trace of some antiseptic substance added. Its antitoxic value is then estimated by testing it in animals against the toxin. An *immunity unit* neutralizes 100 times the minimum lethal dose of toxin, the two being injected simultaneously.

The British Pharmacopœia directs that the official sera shall be sealed into sterilized glass containers and the label or wrapper shall state (1) the name of the product and (2) whether the product is natural serum, antitoxic globulins, or a derivative of antitoxic globulins in liquid or dried form; (3) the date after which the preparation is not intended to be used; (4) the total Units in the container; and (5) the Units in 1 Mil or G. The liquid forms are yellow or yellowish-brown fluids, transparent, but become opalescent with age; the solid forms are yellowish-white powders or yellowish-brown flakes, which in 10 parts of water form solutions resembling the liquid form.

Method of Injection.—Antitoxic sera are injected, with antiseptic precautions, subcutaneously, intravenously or intraspinally. For subcutaneous injection the flank, lower abdomen, buttock, or any part with loose subcutaneous tissue is selected. Not more than 20 c.c. should be injected in one place. Intravenous injection is made at the bend of the elbow; it has the great advantage of saving time (about 8 hours) in critical cases.

Toxinum Diphthericum Diagnosticum.—Schick Test Toxin. A sterile filtrate from a broth culture of Corynebacterium diphtheriæ diluted before use so that 0·2 Mil shall contain the test dose. The diluting fluid is either Sterile Isotonic Sodium Chloride or a 1·5 per cent. aqueous solution of a mixture of Borax 57, Boric Acid 85, and Sodium Chloride

99 parts; in the former solution, stability lasts a few days, in the latter, two months.

Dose.—*By intradermal injection:*
Metric, 0·2 Mil; Imperial, 3 min.

Toxinum Diphthericum Calefactum.—Schick Control. Schick Test Toxin heated to 70° C. for 5 minutes; it is issued with the same batch of toxin from which it was made.

Dose.—*By intradermal injection:*
Metric, 0·2 Mil; Imperial, 3 min.

USES

The Schick Test is used to diagnose immunity or susceptibility to diphtheria.

Schick Test.—Inject intradermally 0·2 Mil of Schick Test Toxin into the right arm and, as a control, 0·2 Mil of the heated Toxin into the left arm. After 24 hours or, better, on the third day the results are estimated. If both arms show no more than a needle wound, the reaction is negative and the case immune; if the left arm shows no reaction but the right exhibits a hyperæmic area about 2 to 3 cm. in diameter, the reaction is positive and the case susceptible: if both arms exhibit a hyperæmic area with a darker red centre, this is a pseudo-reaction and the case immune —a pseudo-reaction is due to some other protein. Rarely a positive reaction may be superposed upon a pseudo-reaction. Cases which are susceptible should be treated with Diphtheria Prophylactic.

Toxinum Diphthericum Detoxicatum.—Diphtheria Prophylactic. This is diphtheria toxin (the sterile filtrate of a culture of Corynebacterium diphtheriæ) or material derived therefrom, its specific toxicity being either reduced to a low level or removed by chemical substances; diphtheria antitoxin may or may not have been added.

CHARACTERS.—Diphtheria Prophylactic occurs in the following and other forms:

1. **Formol Toxoid (F.T.) or Anatoxin.**—A clear liquid, prepared by Formaldehyde.
Dose.—*By intramuscular injection:* The volume indicated on the label as the dose on 2 occasions at an interval of not less than 4 weeks, and a 3rd, if used, at an interval of not less than 2 weeks.
2. **Alum Precipitated Toxoid** (A.P.T.).—A suspension of white or yellowish particles in a colourless liquid, prepared by adding Alum to Formol Toxoid.
Dose.—*By intramuscular injection:* First dose, 0·2 to 0·5 Mil, followed after 4 weeks by a second dose of 0·5 Mil.
3. **Toxoid-Antitoxin Mixture (T.A.M.).**—A clear liquid, prepared by Formaldehyde with Diphtheria Antitoxin added.

Dose.—*By intramuscular injection:* Three doses of 1 Mil, the second given not less than 4 weeks after the first, and the third not less than 2 weeks after the second.

4. **Toxoid-Antitoxin Floccules (T.A.F.).**—A suspension of white particles in a colourless liquid, prepared by Formaldehyde with Diphtheria Antitoxin (80%) of Toxoid added.

Dose.—*By intramuscular injection:* Three doses of 1 Mil, the second given not less than 4 weeks after the first, and the third not less than 2 weeks after the second.

ASSAY.—By the degree of immunity conferred on guinea-pigs against Schick Test toxin.

USES

Injections, usually given in the deltoid region, of Diphtheria Prophylactic are **protective** against diphtheria; the immunity develops slowly during some weeks and is lasting, but a further dose may be advised after 4 years in children. The commonly used forms are A.P.T. and T.A.F. Reactions are rarely severe in children from ages one to ten. F.T. causes severe reactions and is no longer used; A.P.T. should not be given to older children or adults; for them T.A.F. is least liable to produce reactions; P.T.A.P. (Purified Toxoid Aluminium Phosphate Precipitated) rarely causes reactions but gives satisfactory immunity. T.A.M. is the least satisfactory prophylactic.

Antitoxinum Diphthericum.—Diphtheria Antitoxin. A serum, or a preparation from serum, containing the antitoxic globulins having the specific power of neutralizing the toxin formed by Corynebacterium diphtheriæ.

Liquid Preparations contain not less than 500 Units per Mil, and *Solid* not less than 5,000 Units per G. Antitoxin deteriorates rapidly at first, then more slowly if kept cool; the date after which it should not be used is on the label.

CHARACTERS.—Liquid forms are yellow or yellowish-brown, transparent, becoming opalescent with age. Solid forms are yellowish powders or flakes which in 10 parts of water form solutions resembling the liquid form.

ASSAY.—By estimating the amount of the antitoxin which in guinea-pigs will neutralize the same amount of toxin as does 1 Unit of the standard antitoxin kept at the National Institute of Medical Research.

Dose.—*By injection:*

Prophylactic, 500 to 2,000 Units.
Therapeutic, not less than 10,000 Units.

USES

Diphtheria Antitoxin is valuable as a rapid prophylactic for those who have been in contact with the disease; its effect lasts about 14 days.

As a remedial agent it is essential that it should be **given as early as possible**—even before bacteriological confirmation—and in large doses. Given intravenously it reaches the tissues much more rapidly than when it has to be absorbed from an intramuscular or subcutaneous injection. In moderate cases, 10,000 to 30,000 Units are given intramuscularly in the flank or between the scapulæ; in severe cases, or if the case is not seen till the second or third day, 30,000 to 100,000 Units are required intramuscularly or 10,000 to 50,000 Units intravenously. Large doses can be given by using high-potency serum containing 2,500 Units per Mil.

Antitoxin administration checks the extension of the membrane which soon becomes detached, the clinical symptoms improve and the cardiac and nervous complications are prevented or minimized while the mortality rate of the disease is greatly reduced.

Antitoxinum Tetanicum.—Tetanus Antitoxin. A serum, or a preparation from serum containing the antitoxic globulins having the specific power of neutralizing the toxin formed by B. tetani. For *prophylactic use*, a potency of 1,000 Units per Mil in liquid, and 10,000 Units per G in solid preparations is required; for *therapeutic use*, 5,000 Units per Mil in liquid, and 50,000 Units per G in solid preparations.

CHARACTERS.—Similar to those of Diphtheria Antitoxin.

ASSAY.—Similar to the method used for Diphtheria Antitoxin, using guinea-pigs or mice.

Doses.—*By injection:*

Prophylactic, not less than 3,000 Units.
Therapeutic, not less than 100,000 Units.

USES

Tetanus antitoxin is a **valuable prophylactic** when wounds are incurred in areas infected by tetanus and it is advisable as a precautionary measure; it is given intramuscularly and as its protective value reaches a maximum in three days and then declines, three additional weekly injections are advisable; for large wounds, 9,000 Units are given. As a therapeutic agent it is **curative** in early cases if it is injected in large doses of 200,000 Units intravenously; 50,000 Units intrathecally on the first two days is advised by some; subsequent doses may be intramuscular until symptoms subside.

Toxinum Tetanicum Detoxicatum.—Tetanus Toxoid. Tetanus Toxin (the sterile filtrate of a culture on a suitable medium of Clostridium tetani), the specific toxicity having been completely removed, but retaining efficient properties as an immunizing antigen. It occurs as (*a*) Tetanus Toxoid, treated by Formaldehyde, in simple solution;

(*b*) Alum Precipitated Tetanus Toxoid suspended in Injection of Sodium Chloride.

CHARACTERS.—Simple solution: a clear yellow or colourless fluid; Alum Precipitated Toxoid: a suspension of white or yellowish particles.

Dose.—*By subcutaneous or intramuscular injection:* A first dose of **0·5 to 1 Mil (8 to 15 mins.)**, followed after an interval of not less than six weeks by a second dose of **1 Mil (15 mins)**. (Unless Alum Precipitated Tetanus Toxoid is specified, Tetanus Toxoid in simple solution shall be dispensed).

USES

Tetanus Toxoid is an effective prophylactic. Tetanus Toxoid in simple solution may be given subcutaneously, but the Alum Precipitated suspension is given intramuscularly as, subcutaneously, it causes skin nodules. The immunity lasts a year or more, and it is used for persons liable to wounds in areas where the soil is infected. It may be given at the same time as T.A.B. vaccine.

Toxinum Staphylococcicum Detoxicatum.—Staphylococcus Toxoid. Staphylococcus toxin (the sterile filtrate of a culture of a toxigenic strain of Staphylococcus), the specific toxicity being reduced to a low value, but retaining efficient properties as an immunizing antigen.

CHARACTERS.—Undiluted: a pale-yellow liquid.

Dose.—*By intramuscular injection:* Metric, **0·05 Mil** (Imperial, **3/4 min.**) gradually increased to **1 Mil (15 mins.)** at intervals of 4 to 7 days.

USES

It is used in the treatment of recurrent boils and carbuncles and in resistant chronic staphylococcic infections.

Antitoxinum Welchicum.—Gas-gangrene antitoxin (perfringens). A serum, or a preparation of serum containing the antitoxic globulins having the specific power of neutralizing the toxin formed by Clostridium perfringens (B. Welchii, Type A). Liquid preparations contain not less than 250 Units per Mil, solid, 2,500 Units per G.

ASSAY.—Similar to that used for Diphtheria Antitoxin, using mice.

Doses.—*By injection:*

Prophylactic, 10,000 Units.
Therapeutic, not less than 30,000 Units intravenously.

USES

Prophylactic doses are given intramuscularly for the **prevention of gas gangrene** in wounds and after acute intestinal obstruction or appendicitis. Therapeutic doses are used in the treatment of gas gangrene and in **cases of intestinal toxæmia** and paralysis, characterized by vomiting (often fæcal), distension of the intestines and rapid, weak pulse. After the initial intravenous dose, it is advisable to give 4,000 to 10,000 Units every 6 hours intramuscularly.

Antitoxinum Œdematiens.—Gas-gangrene Antitoxin (œdematiens). A serum, or a preparation of serum containing the antitoxic globulins having the specific power of neutralizing the toxin formed by Clostridium œdematiens. Liquid preparations contain not less than 1,500 Units per Mil, solid, 15,000 Units per G.

ASSAY.—By comparison of its neutralizing power upon the toxin's lethal action in mice, or local œdema and necrosis on intracutaneous injection in guinea-pigs.

Doses.—*By injection:*

Prophylactic, 10,000 Units.
Therapeutic, not less than 30,000 Units.

USES

For the prevention and treatment of gas gangrene due to this organism in wounds.

Antitoxinum Septicum.—Gas-gangrene Antitoxin (Vibrion septique). A serum, or a preparation of serum containing the antitoxic globulins, having the specific power of neutralizing the toxin formed by the Clostridium septicum.

ASSAY.—As for Antitoxinum œdematiens.

Doses.—*By injection:*

Prophylactic, 5,000 Units.
Therapeutic, not less than 15,000 Units.

USES

For the prevention and treatment of gas gangrene due to this organism in wounds.

Antitoxinum Œdematiens Compositum.—Mixed Gas-gangrene Antitoxin. Liquid Preparations have a potency of Gas-gangrene Antitoxins not less than 1,000 Units (œdematiens), 1,000 Units (perfringens), and 500 Units (septicum) per Mil.

Dose.—*By injection, not less than:*

Prophylactic: **10,000 Units** (œdematiens), **10,000 Units** (perfringens), and **5,000 Units** (septicum).
Therapeutic: **30,000 Units** (œdematiens), **30,000 Units** (perfringens), and **15,000 Units** (septicum).

USES

As a prophylactic, the mixed antitoxin is injected intravenously or intramuscularly as early as possible and altered to the specific antitoxin if the organism is identified. The therapeutic dose is given intravenously for speedy action and may be repeated every six hours, if necessary.

Serum Antidysentericum (Shiga).—Antidysenteric Serum (Shiga). Shigella shigæ or B. dysenteriæ (Shiga).

Dose.—*By injection:*
Therapeutic: **200,000 Units, repeated if necessary.**

USES

This serum is given intravenously or intramuscularly to mitigate the toxæmia in severe bacillary dysentery (Shiga) in addition to oral Sulphonamides and in cases resistant to these drugs.

Streptococcus Toxin (Scarlatina).—Scarlet Fever Prophylactic. The sterile filtrate from a broth culture of Streptococcus hæmolyticus scarlatinæ, made in two strengths: (1) containing 2,500 skin-test doses per Mil; (2) containing 20,000 skin-test doses per Mil.

Dose.—500 skin-test doses increasing to 1,000, 5,000 and 10,000 at weekly intervals, or 1,000, 5,000 and 20,000 skin-test doses at fortnightly intervals.

USES

Scarlet Fever Prophylactic is valuable as a **protective** for contacts amongst children and nurses; the immunity lasts a considerable time—not so long as that to diphtheria—therefore, in an epidemic, it should be confirmed by the Dick Test.

Dick Test.—This corresponds with the Schick Test. Intradermal injection of 0·2 Mil of a dilute scarlet fever toxin and of its heated control is used. Susceptible persons and early cases of scarlet fever give a positive reaction.

Scarlet Fever Antitoxin.—A serum containing the antitoxic globulins having the specific power of neutralizing the erythrogenic, or scarlet fever, toxin formed by certain strains of Streptococcus pyogenes (S. hæmolyticus scarlatinæ).

Dose.—*Prophylactic*, 1,500 to 3,000 Units. *Therapeutic*, 3,000 to 30,000 Units intramuscularly or in urgent cases intravenously.

USES

This serum should be **given as early as possible** in scarlet fever; the rash, temperature and throat symptoms generally subside in 2 days, convalescence is rapid and patients may be discharged in about 3 weeks; it reduces the incidence of complications. The dose may be repeated in 2 days if necessary. The antitoxin is also a valuable **prophylactic** during epidemics.

Blanching Test (Schultz-Charlton).—Intradermal injection of 0·2 Mil of a 1 : 10 dilution of Scarlet Fever Antitoxin into the skin of a scarlet fever patient causes local blanching in 8 to 24 hours; a negative result does not absolutely exclude scarlet fever.

Immune Human Measles Serum. Measles Convalescent Serum.—Serum from convalescing patients taken 6 to 9 days after they are afebrile.

Dose.—*Prophylactic or for attenuation:* 2·5 to 10 Mils *by intramuscular injection.*

USES

If given before the fifth day after infection, it may prevent an attack; if after, the attack is attenuated or mitigated. An attenuated attack gives later an active immunity, but prevention gives only a passive immunity lasting about a month. Post-inoculation serum hepatitis is a considerable risk, hence whole compatible blood (10 to 15 Mils), e.g. from a parent, is often used although this leaves hæmatomata.

Rabies Antitoxin.—An emulsion made from the spinal cords of rabbits inoculated with the virus from a rabid animal.

Dose.—Injections are given of emulsions containing increasing strengths of the virus.

USES

It is curative in rabies if given early. Virus inactivated by 1 per cent. Phenol or attenuated by treatment with Ether is now used.

Anti-Venom Serum.—The serum of animals, or a preparation of it, containing the antitoxic globulins having the power of neutralizing various snake venoms.

Dose.—*Therapeutic:* 20 to 30 Mils, *intravenously in repeated doses.*

USES

Snake venoms contain neurotoxins (cobra, mamba), and hæmotoxins (viper, rattlesnake), but the toxins of different snakes are not similar; hence a mono-valent serum, if available and the species recognized, is best. It should be given intravenously in large doses within an hour of the bite, and 2 to 3 Mils locally in addition to incision and ligature.

Russell Viper Venom.—Stypven. Rusven. The venom of Vipera Russellii, the daboia viper of India, is the most rapid coagulant of both normal and hæmophilic blood. A sterile dilute solution (1:10,000) is successful as a local application after tonsillectomy or nasal operations and, soaked in cotton-wool plugs, to check bleeding from tooth-sockets in hæmophiliacs. It must not be injected.

Normal Horse Serum.—This was used locally to arrest hæmorrhage, and injected subcutaneously (10 Mils) in hæmorrhages with a view to increasing the coagulability of the blood; its efficacy is doubtful.

Hæmoplastin, *Hæmostyl*, *Coagulose* and *Hæmostatic Sera* are obtained from horses during the regenerative phase after a hæmorrhage and have been given orally or hypodermically for persistent hæmorrhage. *Protagulin* is a dried fibrin ferment which is dissolved in 1 Mil of saline and applied to a bleeding surface. *Thromboplastin* is an extract of kephalin from the brain applied to bleeding surfaces on the principle that thrombokinase is related to kephalin. The therapeutic value of all of these is unreliable.

Anaphylaxis (Allergy) is a sensitive condition arising from the injection of foreign proteins. A small initial dose of protein will cause sensitization, and if, after 10 days, a large amount of the same protein is injected, especially intravenously, symptoms of restlessness, rigor and pyrexia, emesis, diarrhœa, asthmatic attacks from bronchial spasm and œdema of the bronchial mucosa, cyanosis or pallor, weak pulse and circulatory collapse may occur within 1/2 to 3 hours (anaphylactic shock). The reaction is specific for the sensitizing protein, and can be shown on isolated organs, e.g. uterus and bronchioles of guinea-pig, which are powerfully contracted. Anaphylactic shock is rarely serious in man, and recovery may occur in a few minutes, after profuse sweating; more frequently a sensitivity to the foreign serum has to be feared and, if intravenous injection be necessary, a small dose should be given at first and a further injection only after an interval of half to one hour. Anaphylaxis may be averted by injecting intramuscularly 0·5 Mil (8 min). of Injectio Adrenalinæ after a large intravenous dose of serum.

Serum Sickness.—Occasionally, cutaneous rashes, articular pains and a rise of temperature may be observed, usually on the seventh to the fourteenth day; they may be treated by antihistaminic drugs with anodyne antipyretics for the joint pains and fever.

Desensitization to Sera.—Patients who are sensitive to sera can be desensitized by injecting intravenously, diluted with 9 volumes of Normal Saline, first 0·1 Mil of serum, then at intervals of two or three minutes, if there are no reactions, three further doses of 0·3 Mil, 1 Mil and 2·5 Mils; the patient will then be able to tolerate large doses of the undiluted serum.

Protein Therapy.—Some individuals develop attacks of asthma, hay fever, vaso-motor rhinitis, urticaria, or eczema in response to special proteins, pollens, etc. Various protein test solutions are applied to the forearm and the skin scratched; a positive reaction is shown in a few seconds by hyperæmia followed by a local urticaria. The phenomena are comparable with anaphylaxis. Treatment involves avoidance of the protein; or desensitization of the patient can be attained by injecting a non-specific protein, namely a 5% solution of specially prepared peptone, intramuscularly or intravenously in doses graded from 0·3 to 1·5 Mils (5 to 25 min.) every 4 to 5 days.

These allergic conditions are usually greatly benefited by the antihistamine drugs Anthisan, Benadryl and Antistin (*see* p. 382) but relatively few cases of asthma respond to these drugs.

Hay-fever vaccine, an extract of pollen toxins, is given subcutaneously; the initial dose should be ascertained first by the intradermal reaction; and then increased every 7 days till 100,000 Units is reached. Treatment should start in the early days of spring.

Thrombin (Human).—The enzyme, which converts Fibrinogen into fibrin, is a cream-coloured powder, forming an opalescent solution in

Normal Saline. One Unit clots 1 Mil of a 0·1 % saline solution of Human Fibrinogen in 15 seconds at 37° C.

USES

It is available in containers holding 50 Units for plastic surgery, and 500 Units for use with Fibrin Foam. When used with Fibrinogen, the strength used depends on the required rapidity of clotting; when used with Fibrin Foam, a solution of 30 to 50 Units per Mil is usual.

Fibrinogen (Human).—The soluble protein of plasma, which, on adding Thrombin, is converted to the insoluble protein Fibrin; it is a white powder, soluble in Injection of Sodium Chloride, but fibrin deposits gradually; solutions, being unstable, are prepared immediately before use.

USES

Fibrinogen is used as a 1 or 2 per cent. solution to promote adhesions of skin-grafts, and with Thrombin to hasten clotting and fixation of nerve sutures; the clot strength depends on the fibrinogen concentration. It is also injected intravenously (10 Mils of a 2 per cent. solution) to reduce for 24 to 36 hours the clotting time in hæmophilia.

Fibrin Foam (Human).—An insoluble foam made by adding Thrombin to a foamed 1% saline solution of Fibrinogen. It is a light, white, spongy material. Fibrin Film is made by clotting Fibrinogen with Thrombin and forms thin transparent sheets.

USES

Fibrin Foam with Thrombin is used as a hæmostatic in chest and brain surgery; a portion of foam, soaked in a solution of Thrombin, is placed on the bleeding position; blood coagulates on it immediately and it is left to be absorbed. Fibrin Film is used to repair the dura mater in brain surgery.

Hyaluronidase.—Hyalase. A mucolytic enzyme, which reduces the viscosity of hyaluronic acid, a mucopolysaccarhide, which is a tissue-cement substance. *Dose.*—1 mg (1/60 gr) or 1,000 Units dissolved in 1 Mil of distilled water. Hyaluronidase, when added to injection fluids, accelerates their diffusion into the surrounding tissues without causing swelling. It obviates intravenous injection of Normal Saline, particularly in dehydrated children and increases the area of anæsthesia from local anæsthetics.

PART III

GENERAL THERAPEUTICS

CHAPTER I

THE FOUNDATIONS OF RATIONAL TREATMENT

THE physician, in order to prescribe appropriate treatment for diseases, must possess an intimate knowledge of (1) the physiological principles concerned in maintaining health and in compensating for abnormal circumstances; (2) the ætiology and pathology of the disease; (3) the effects produced by drugs and other remedial agents upon the various tissues of the normal organism; and (4) the curative or palliative effects of drugs and other means of treatment upon diseases and their symptoms. A brief discussion of these factors will indicate their relative importance and interdependence.

1. **Health.**—This implies a normal or physiological state of the body and its vital organs. A normal state of health is a variable physiological resultant of the functions of the body in response to the varying influences to which a person is exposed. The body can adjust itself to widely differing influences and environments, e.g. modification of diet, of external temperature and of physical exertion; and can protect itself with variable success against organismal invasion. But if, for example, some vital organ fails to perform its functions adequately from structural or functional change, or if the physiological means of compensation for increased work by the organ break down, or if the protective mechanisms of the body are inadequate to overcome an invading micro-organism, then a departure from the state of health results and symptoms indicative of the abnormal condition or "disease" appear. Minor disturbances of the average physiological conditions in the body render it extremely difficult, however, to draw a sharp line of distinction between the states of health and disease.

2. **Ætiology and Pathology.**—A knowledge of the ætiology, or cause, and of the pathological changes which occur in the struc-

ture or functions of the tissues in diseased conditions, is of primary importance for treatment because this knowledge enables the relative value of symptoms to be estimated properly. The symptom "diarrhœa," for example, may be due to unsuitable food, or to a highly sensitive nervous reflex; but dysentery, typhoid, etc., must be excluded as alternative causes before appropriate treatment can be decided. Again, cough in association with profuse expectoration is a beneficial reflex which should not be checked; but, if there is little sputum and the cough is painful or prevents sleep, it is then permissible to diminish it by drugs.

3. **Applied Pharmacology.**—A knowledge of the effects of drugs upon normal tissues is of great importance because most commonly it is their actions upon normal tissues that we wish to utilize; in fact, drugs often fail to produce their typical effects upon tissues which have undergone pathological change. Cocaine, for instance, may not relieve pain in inflamed tissues and Atropine may fail to dilate the pupil in iritis. Instances of the use of drugs because of their actions upon normal tissues are: remedies producing effects by reflex means, e.g. bitters, expectorants, etc.; remedies influencing the normal nervous system, e.g. anæsthetics, central anodynes, hypnotics, medullary stimulants and depressants, etc. Drugs acting on the intestine, bronchioles and uterus are dependent usually upon the normality of the local nervous mechanism or involuntary muscle, and the therapeutic value of cardiac stimulants and diuretics is also influenced by the amount of undamaged tissues in these organs.

The therapeutist must be conversant not only with the chief actions and uses of a drug, but also with its side-effects and possibly undesirable influences upon other tissues of the body: for example, Morphine, which relieves pain, also depresses the respiratory centre and causes constipation; Cinchophen, which augments the excretion of uric acid, may cause acute necrosis of the liver; and Neoarsphenamine, used in syphilis, may cause symptoms of arsenical poisoning. A thorough acquaintance with the actions of drugs enables one to avoid most of these unwanted effects by restricting or spacing the dosage, by varying the method of administration, by substituting another drug having less undesirable side-effects, or by combining the drug with another which will counteract the undesirable actions.

4. *Therapeutics.*—The art of therapeutics or treatment is essentially the application of pharmacology. Its ideal is to achieve for each disease a specific remedial agent. The advances towards this

goal have been remarkable within recent times: the Organic Arsenic and Bismuth preparations in syphilis; Antimony compounds in trypanosomiasis; Emetine in amœbic dysentery; Insulin in diabetes mellitus; Liver Extracts in pernicious anæmia; Vitamin D in rickets; Sulphonamides and Penicillin in many organismal infections; Streptomycin in tuberculosis; and vaccines or antitoxins in the prevention and treatment of organismal diseases are some examples of the control which has been gained over diseases by means of drugs. There are, however, no specific remedies for many common diseases which must, therefore, be treated symptomatically.

Rational therapeutics implies either the use of the specific remedy for a disease or, broadly speaking, the employment of drugs or other agents which will mitigate the injurious and exhausting symptoms, e.g. pain, fever, restlessness, of a disease so as to conserve the strength of the patient and enhance his natural powers of resistance and recovery. The natural recuperative powers of the body are exhibited, for example, in the development of agglutinins or bacteriolysins in the blood to combat bacterial invasion and in the hypertrophy of heart muscle to compensate for a defective valve. The following principles of treatment are included in the conception of rational therapeutics:

(1) *Preventive Treatment.*—The science of preserving health is known as *Hygiene* or *Preventive Medicine.* Hygienic principles, e.g. pure water, sound food, sanitation, cleanliness, etc., have been instrumental in eradicating many epidemic diseases and in improving the health of the community. Under this heading, advances have been made in the eradication of such disease vectors as mosquitoes for malaria and lice for typhus by the use of insecticides, such as Dicophane.

(2) *Prophylactic Treatment.*—This is practicable in some diseases of which we know the cause. Prophylaxis means the prevention of disease in those who have been exposed to infection or to unhygienic circumstances which may induce a liability to that disease. Examples of prophylactic treatment are the use of vaccines against smallpox and typhoid, of sera against diphtheria and tetanus, of vitamins against rickets, scurvy and beri-beri, of Quinine or Mepacrine as suppressives of malaria, and of Sulphonamides or Penicillin as preventives of general septicæmia from operations or wounds in infected areas.

(3) *Remedial Treatment.*—When disease is established treatment must be directed towards curing the complaint or, if this is

impossible, to alleviating its prominent symptoms and to conserving the vital functions of the body. It is important for the student to realize that remedial treatment does not imply solely the use of specifically curative drugs, but also the utilization of every means which may promote the comfort, maintain the strength and hasten the recovery of the patient. Effective remedial treatment of disease necessitates giving advice upon the hygiene, temperature and ventilation of the patient's surroundings, upon his position in bed and his bed-clothing, and also upon dietetics, so that his circumstances become such as will conduce to his return to normal health. The particular method of treatment considered appropriate may in some cases be surgical, physical (massage and exercises), or in other instances by means of drugs.

Ætiological Treatment.—It is clearly rational to eradicate the cause of a disease, if this be possible; gastric pain due to unsuitable food or poison demands a prompt emetic; diarrhœa due to irritant matter in the intestine requires a purgative to expedite its removal; localized bacterial infections and parasitic skin diseases must be treated by the use of antiseptics superficially; syphilitic infection must be combated by intramuscular injections of Penicillin and by intravenous injections of the organic compounds of Arsenic so as to kill the parasite; and Vitamins are supplied to treat deficiency diseases.

Specific Treatment.—This implies the use of a remedy which has a definite curative effect upon a disease; it is clear that drugs which eradicate the cause of a disease will also belong to this category. But this term is also applicable to the treatment of diphtheria by antitoxin, which neutralizes the toxin formed by the bacteria. Specific treatment is still in some instances *empirical,* that is to say, we are unable to explain why the remedy is successful although clinical experience has proved its value; the use of Salicylates in acute rheumatism and of Colchicum in acute gout are examples of empirical treatment.

Palliative Treatment.—This implies the use of remedies to mitigate the symptoms of a disease for which we have no specific remedy and, therefore, it is often referred to as *symptomatic*—or in some circumstances, *expectant—treatment.* We have no specific remedy for many pulmonary infections, yet we can relieve fever in these by means of antipyretics, and troublesome cough by means of expectorants or depressants to the respiratory centre. Phenobarbitone, Methyl Phenobarbitone, Phenytoin, and Bromides are palliative in epilepsy and Digitalis will re-establish an efficient ventricular beat and circulation in auricular fibrillation without curing the fibrillation which originated the circulatory failure.

Plan of the following chapters.—The object of this section of the book is to present a brief survey of the essential pharmacological actions of drugs upon the various systems of the body and from these to deduce the rational therapeutic applications of these drugs in the treatment of diseases or in the alleviation of symptoms.

CHAPTER II

DIGESTION—THE MOUTH

PHARMACOLOGY

WE must first consider what means are at our disposal for influencing the physiological functions of the mouth and for restoring these when they are disordered.

1. **Food.**—The chief principles of foods are proteins, carbohydrates, fats, salts, vitamins and water. The relative proportions of these constituents vary greatly in different foods and for this reason we may desire to modify the diet in many diseases according to some system of dietetics (*see* p. 591). In the mouth, the pleasant taste of food excites the taste buds and reflexly produces a flow of saliva, which acts as a lubricant to the bolus and, by means of the enzyme diastase, converts some of the starch into maltose and dextrin. Unappetizing food may inhibit salivary secretion and thus retard the ability to swallow an unwelcome bolus.

The *character of the food* is also important. Soft foods which demand little mastication doubtless contribute to the development of caries, whereas meat, vegetables and solid fruits, which must be chewed, act both as mechanical detergents to the teeth and also as stimulants to the secretion of the alkaline saliva which will check acid fermentation.

An adequate supply of Vitamin D and Calcium Salts in the diet is essential for the effective *calcification of the teeth* in children and as a prophylactic against caries. Deficiency of these prophylactic agents in the mother's diet during pregnancy may have deleterious effects upon the teeth and bones of both the mother and the child. Sufficient supplies of Vitamin D can be ensured by supplying whole milk, butter, Cod-liver Oil or Calciferol, but it should be noted that, of these, only whole milk contains more than traces of Calcium salts which may, therefore, have to be supplied by adding meats or their juices, vegetables or Calcium salts to the diet.

2. **The sensory nerves of taste and of sensation** in the mouth are derived from the lingual and glosso-pharyngeal nerves and can be influenced by many agents. Stimulants of the taste buds on the tongue produce useful pharmacological effects. Firstly, they increase relish for, or enjoyment of, food and thus improve the appetite; secondly, they excite reflexly the secretion of saliva and of the gastric juices. Apart from the characteristic flavours of foods, many aromatic *volatile oils*, e.g. Cinnamon and Mustard; *pungents*, e.g. Ginger; or *acids*, e.g. vinegar and lemon juice, are active stimulants to the taste buds; therefore, the art of cookery, the use of condiments, such as pickles and sauces, and the selection of wines, depend for their success upon the excitation of the taste buds, as well as of the sense of smell.

The official *stimulants to the taste buds* are large in number and varied in taste. They have two useful actions: (1) those which are pleasantly aromatic or sweet are used to mask the unpleasant taste of other remedies and mixtures, and to impart an agreeable flavour or aroma to medicines, whether for internal or external use; (2) aromatic, bitter and acid substances produce reflexly an increased flow of saliva and of gastric juice, which will improve the digestion of food. It must be clearly understood that these actions will be obtained most satisfactorily from solutions of the appropriate drugs and, therefore, the Pharmacopœia provides mainly dilute aqueous and concentrated spirituous preparations of flavouring agents and bitters.

The drugs which are used as **gustatory stimulants** may be arranged as follows:—

(1) *Volatile Oil Series.*—Anise, Dill, Peppermint, Cinnamon, Caraway, Clove, Coriander, Cardamom and Nutmeg are used chiefly as flavouring agents and are prescribed variously in the form of an Aqua Destillata, Aqua Concentrata, Spiritus, Tinctura or as the Oleum distilled from the plant. Each has its own characteristic flavour and this enables the patients' preference to be considered.

(2) *Simple Bitters.*—Quassia, Calumba, Quinine and Strychnine have a purely bitter taste and this unusual stimulus to the taste buds excites reflexly a marked increase in the salivary and gastric secretions; later, the contrast of the pleasant taste of food taken afterwards stimulates a further flow. Bitters are, therefore, selected particularly when the gustatory reflex is defective and should be administered in solution shortly before meals. Bitters have little action when the reflex is normal in activity. Quassia and

Calumba may be prescribed as the Infusum, Infusum Recens or Infusum Concentratum and as Tinctures. Quinine and Strychnine are used when their important actions after absorption are also required.

(3) *Aromatic Bitters.*—Gentian and Bitter Orange Peel, which contain both aromatic and bitter constituents, are somewhat less effective in action than Simple Bitters but more pleasant to take as Infusions or Tinctures.

(4) *Pungent Substances.*—These, e.g. Ginger, produce a more powerful irritation of the taste buds and sensory endings in the mouth than the Volatile Oils.

(5) *Sweetening Agents.*—These include Sucrose, Dextrose, Glucose, Lactose and Lævulose, which are carbohydrates; Saccharin Sodium and Glycerin. Of these, Saccharin Sodium is a suitable sweetening agent for diabetic foods.

(6) *Weak Acids.*—Acid fruits (lemon juice), Citric, Tartaric or Acetic Acid and Acid Potassium Tartrate are suitable for use, but the Dilute Mineral Acids are unsuitable because they attack the enamel of the teeth.

(7) *Alcoholic Solutions.*—These are the various spirits, tinctures, and aromatic wines; preparations of Chloroform and Ether act similarly.

Lastly in this section it should be noted that use is made of the *unpleasant taste and smell* of Valerian, as Tinctura Valerianæ Ammoniata, to produce, by an unusual stimulation of the taste buds, a reflex psychic influence upon the higher cerebral centres in the treatment of hysteria.

3. **Sialagogues.**—These are drugs which increase the flow of saliva; they also increase the secretion of the mucous glands in the mouth. Sialagogues may be classified according to the method of their action: (1) Many drugs produce a flow of saliva by reflex nervous action. This may arise in two ways—(*a*) from stimulation of the sensory nerves of taste or smell by aromatic substances, bitters, pungents, dilute acids, acid salts and acid juices, e.g. lemon juice, as well as by Ether, Chloroform and Alcohol; (*b*) from stimulation of the sensory vagus endings in the stomach by irritants—a characteristic action of the reflex emetics, such as Ipecacuanha. (2) Nicotine, Lobeline and Coniine, in small doses, increase the saliva by stimulating the nerve cells in the secretory ganglia (otic, submaxillary and sublingual ganglia). (3) Parasympathetic stimulants or cholinergic drugs cause salivation by stimulating the secretory nerve endings of the chorda tympani or

glosso-pharyngeal, e.g. Acetylcholine, Carbachol, Physostigmine, Neostigmine, Pilocarpine and Muscarine. (4) Some drugs act by direct stimulation of the secretory cells during their excretion; the salivation induced by continued dosage with Mercurial salts and Iodides is produced in this manner. Only those sialagogues which act reflexly by stimulating the taste buds are in common use therapeutically to augment salivary secretion.

4. **Antisialagogues.**—The salivary secretion may be reduced in different ways: (1) by reflex action, for example, insipid or unpalatable foods or medicines reflexly inhibit the secretion; (2) by mechanical action, e.g. demulcents, dilute alkalis or soapy substances, since they lubricate and form over the mucous membrane a protective coating which renders salivary secretion, for a brief period, superfluous; (3) toxic doses of Nicotine, Lobeline and Coniine can paralyse the secretory ganglia and so lessen the saliva; (4) by paralysing the secretory nerve endings in the glands, parasympathetic depressants, or antagonists of choline, e.g. the Atropine alkaloids and the drugs containing them—Belladonna, Stramonium and Hyoscyamus—check the secretion; (5) the antisialagogue effect of Morphine is central in origin. The Atropine series are the only suitable drugs for therapeutic purposes.

5. **Demulcents.**—If the flow of saliva be deficient and the mouth dry, demulcents are valuable substitutes for the mucus because they coat the mouth with a mucilaginous protective coating and thus allay thirst. Such are albuminous or mucilaginous drinks, e.g. milk, barley water and gruel, or pastilles made with gelatin and glycerin.

6. **Antiseptics.**—These are generally used in the form of mouth washes and it should be realized that, to be really effective, an antiseptic mouth wash must be used at 2-hourly intervals during the day because salivation soon annuls any immediate action it may have. The pharmacological criteria for an ideal antiseptic in buccal infections are (1) rapidity in bactericidal action; (2) continuity of inhibitory effect on bacterial growth (bacteriostatic action); (3) minimal toxic action upon the mucous membrane; and (4) absence of deleterious effects upon the teeth or fillings. The volatile oils conform most closely to these stringent requirements; but for various reasons many other antiseptics are employed in the treatment of buccal infections:—

(1) *Osmotic Antiseptics.*—Hypertonic Saline (5 per cent.) is non-toxic and dissolves protein residues but softens the gums.

(2) *Oxidizing Antiseptics.*—Hydrogen Peroxide (5 to 10 per

cent.) is non-toxic and the evolution of its oxygen detaches bacteria and debris, but its bactericidal action is weak and brief. Potassium Permanganate (0·02 to 0·1 per cent,) is non-toxic, quickly bactericidal but brief in action and stains the teeth brown. Potassium Chlorate (1 per cent.) as a mouth wash or as tablets or lozenges is an unreliable antiseptic even for mild infections.

(3) *Reducing Antiseptics.*—Sodium Sulphite (5 per cent.), although brief in action, is often effective in aphthous stomatitis.

(4) *Metallic Antiseptics.*—Zinc Sulphate (0·5 to 1 per cent.) Silver Nitrate (0·05 to 0·2 per cent.) and Mercuric Chloride (0·02 to 0·04 per cent.) are toxic; their bactericidal action is slow but maintained, as they are precipitated as albuminates; therefore they are also astringents. Boric Acid (4 per cent.) is not toxic but its activity is weak.

(5) *Halogen Antiseptics.*—Liquor Iodi Mitis is painted undiluted upon localized gingivitis or used diluted (0·05 to 0·1 per cent.) as a mouth wash. Liquor Sodæ Chlorinatæ Chirurgicalis (diluted 1 : 20 to 1 : 10) is cleansing, rapid though brief in action, but unpleasant to taste.

(6) *Phenol Antiseptics.*—Phenol (0·2 to 0·5 per cent.), Creosote (0·5 per cent.) and Liquor Cresolis Saponatus (0·5 to 1 per cent.) are toxic but their action is maintained and they are useful if their local anæsthetic effect be also desired.

(7) *Volatile Oils.*—Thymol, Menthol, Camphor and the Oils of Peppermint, Clove and Cinnamon, in strengths of 0·02 to 0·05 per cent., are common antiseptics in mouth washes and tooth-pastes (1 to 3 per cent.) because their general toxicity is low and they possess a rubefacient action and, later, a local anæsthetic effect.

(8) *Aniline Dyes.*—Proflavine Hemisulphate (0·1 per cent.) as a mouth wash and Gentian Violet or Brilliant Green (0·5 to 2 per cent.) as an aqueous paint are effective antiseptics for gingivitis and septic pockets.

(9) *Sulphonamides.*—Sulphanilamide and Sulphathiazole as dusting powders are employed for jaw fractures, and as pastes, soaked in cotton-wool, for septic tooth sockets.

(10) *Penicillin Lozenges* are convenient and powerful oral antiseptics when allowed to dissolve slowly in the mouth and renewed every two hours; they may cause stomatitis.

Occasionally Liquor Formaldehydi (0·2 per cent.) is used in mouth washes as an antiseptic and to harden the gums.

7. **Antacids.**—These are useful in the mouth to relieve pain arising from acid fermentation at the necks of teeth. Sodium

Bicarbonate is effective but Magnesium Oxide and Hydroxide or Calcium Carbonate are better as the insoluble particles are trapped between the teeth, hence their action is more prolonged. Borax solution (2 per cent.) or the Glycerinum is useful in aphthous stomatitis.

8. **Astringents.**—These, by precipitating proteins, diminish mucous secretions, form a protective coating and harden the gums. Zinc Sulphate is best as it does not stain teeth, but Liquor Ferri Perchloridi (12 per cent.) in Glycerin and also Tannic Acid (1 per cent.) or Trochiscus Krameriæ are frequently employed as oral astringents.

9. **Caustics.**—These must be used with care lest they be swallowed. If Argenti Nitras Induratus be used, a small pellet should be fused on the end of a probe. Copper Sulphate crystals are employed for pyorrhœal pockets but, for routine purposes, Trichloracetic Acid and Lactic Acid are more useful. Chromium Trioxide is used chiefly for Vincent's infection.

10. **Local Anæsthetics.**—(*a*) *Surface Anæsthesia.* The value of drugs which paralyse sensory nerve endings as superficial anæsthetics depends upon their absorbability by mucous membranes. Cocaine Hydrochloride (5 to 10 per cent.) is efficient for the nose and gums, and in small quantities as a spray for the palate and throat, or 1/6 gr. for anæsthetizing the tooth-pulp. Cinchocaine Hydrochloride (1 to 2 per cent.), Butacaine Sulphate (2 to 5 per cent.), Xylocaine (2 per cent.), Orthocaine and Benzocaine (in powder form) are also used. Benzyl Alcohol, Creosote, Chlorbutol, and volatile oils such as Menthol, Clove and Methyl Salicylate are common constituents of dental surface anæsthetics. The use of Tincture of Aconite for this purpose, although common, is hardly justifiable.

(*b*) *Deep Anæsthesia.*—This involves the injection of a sterile solution of a local anæsthetic and is used largely for the painless removal of teeth. The solution commonly used is Injectio Procainæ et Adrenalinæ Fortis, which contains Procaine Hydrochloride 2 per cent. and Liquor Adrenalinæ Hydrochloridi 0·1 per cent. Usually 1/2 Mil of solution is injected close to the alveolus on each side of the root of the tooth; about 5 minutes is allowed for permeation of the anæsthetic through the bony tissue to the nerve. Similar injections are used for nerve blocking of the mandibular nerve.

11. **The secretions of the mouth** can be modified by drugs which in minute amounts are excreted by the salivary and mucous

glands. Thus Iodides, Bromides and Mercurial preparations induce salivation by direct stimulation of the glandular cells and their taste is perceptible in the mouth. Excretion of Arsenic in the mouth causes inflammation of the mucous membrane and often a silvery tongue, while Lead and Bismuth may be deposited in the mucous membrane as sulphides and give rise to a bluish or black line on the gums.

THERAPEUTICS

Secretory Disorders.—Although there may be no local lesion in the mouth, abnormal oral secretions are common in many diseases. *Dryness of the mouth* is a prominent symptom in untreated diabetes mellitus, in azotæmic nephritis and in morphinism; the treatment is that of the underlying cause. In many of these cases it is urgently necessary to relieve dehydration, of which a dry mouth is a leading symptom, by the injection of fluid intravenously or subcutaneously. During fevers, and from other causes of dehydration, the flow of saliva is much diminished with consequent thirst and loss of relish for food; fluids must be given liberally to febrile patients and, when the temperature is considerably raised, iced drinks are an agreeable means of relieving thirst. Owing to the decreased salivary secretion and less mastication, the normal mechanism for cleansing the mouth is defective, hence organismal growth increases, therefore, the toilet of the mouth should receive careful attention, in such cases the tongue, cheeks and gums should be gently swabbed with Glycerin of Borax at frequent intervals. The taste buds may be stimulated by acid drinks such as lemonade, or Imperial Drink, which is made by adding half an ounce each of Acid Potassium Tartrate, Lime Juice and Syrup to two pints of water. Juicy fruits such as grapes, oranges and grape fruit may be recommended. Dryness and an unpleasant taste in the mouth occur also in atonic dyspepsia and may be relieved by prescribing one of the simple or aromatic bitters, such as Quassia, Nux Vomica or Gentian, before meals.

Excessive salivation, occasionally a troublesome symptom during pregnancy, is easily checked by small doses of Atropine or Tincture of Belladonna. Hyoscine Hydrobromide relieves the salivation of chronic encephalitis lethargica as well as the muscular rigidity. Salivation is one of the earliest signs of mercurialism and, as it is due to stomatitis, the regular employment of an antiseptic or astringent mouth wash is essential during mercurial treatment.

The symptom of "fetid breath" may be due to such varied causes as dental caries, pyorrhœa, decomposing secretion in tonsillar crypts, nasopharyngeal or middle-ear disease, pulmonary infections scurvy or dyspepsia, each requiring appropriate but not oral treatment. Breath, smelling of acetone, indicates diabetes or, of ammonia or urine, indicates uræmia.

Bleeding from the gums occurs in lymphocytic leukæmia and purpura hæmorrhagica, in scurvy, and as a result of gingivitis. *Congestion is relieved and the gums hardened by gently swabbing them with an astringent lotion, such as Glycerin of Tannic Acid,* night and morning.

Inflammatory Disorders.—The mouth and its associated structures are not infrequently the seat of local inflammatory conditions of bacterial origin. Stomatitis is treated by the frequent use of one of the mild antiseptic mouth washes, containing, for example, Hydrogen Peroxide, Thymol, Boric Acid or Potassium Chlorate (*see* p. 466), or Penicillin Lozenges may be used. Aphthous patches may be painted with a 1 per cent. solution of Silver Nitrate, Zinc Sulphate or Alum; and swabbing with Glycerin of Borax, or Sodium Sulphite (12 per cent.), will rapidly cure infantile thrush, which is due to the fungus *oïdium albicans* (*monilia candida*). Oral ulcers, papillomata or granulations may call for excision or for the use of caustics. Toughened Silver Nitrate and Chromic, Lactic or Trichloracetic Acids are suitable caustics for use in the mouth. But if Silver Nitrate be chosen, the stick must be held firmly in a holder or, better still, a small piece of the caustic may be fused on the end of a metal rod. Ulceration of the mouth is commonly accompanied by a copious secretion of tenacious mucus; this may be removed by the use of a mouthwash or gargle containing 5 per cent. of Sodium Bicarbonate.

Dental Diseases.—The teeth are especially likely to become carious when the calcium reserves of the body are low. During the period of growth in children and during pregnancy or lactation, much may be done to prevent caries by giving foods rich in Calcium, such as milk, and Vitamin D in liberal quantities. If these foods are not readily taken, the regular administration of Calcium Lactate or Gluconate is desirable. Caries is also favoured by the acid decomposition of carbohydrates at the bases of the teeth, and the use of a dentifrice consisting largely of Chalk or other antacid will counteract this tendency.

Toothache, pending the filling or extraction of the offending tooth, can be temporarily relieved by inserting in the carious cavity a piece of cotton-wool soaked in Oil of Clove, Creosote or Chlorbutol which act as antiseptics and local anæsthetics, or, if it is due to inflammation of the pulp, or sepsis at the root, by painting the gum with Liquor Iodi Mitis and by giving Acetyl-Salicylic Acid or Phenacetin.

Pyorrhœa alveolaris requires surgical removal of necrosed tissue and antiseptic, or even caustic, treatment of the suppurating pockets with Copper Sulphate. When teeth with septic roots have to be removed, it is desirable to give prophylactic doses of Penicillin or Sulphonamides several hours before and for a day after the operation to obviate the risk of septicæmia; they also mitigate the oral inflammatory reaction and accelerate healing.

Tonsillitis.—The tonsils are often a gateway for bacterial invasion of the body. Adequate treatment of acute or chronic tonsillitis is important as a preventive of pulmonary and other diseases; and includes attention to rhinitis and sinusitis from which the tonsillar infection often originates. The subject of an acute tonsillitis should be confined to bed. A semi-solid diet consisting of gruel and jellies is generally more acceptable and easily swallowed than a fluid one. It is customary to order a gargle containing Phenol 0·2 per cent., Potassium Chlorate 1 to 2 per cent., or other suitable antiseptic, e.g. Glycerinum Thymolis Compositum (B.P.C.), but gargling usually allows access of the antiseptic only to the anterior pillars of the fauces; therefore, it is more efficacious to paint the tonsils with Pigmentum Iodi Co. (B.P.C.), (Iodine, gr. v, Potassium Iodide, gr. xii, and Oil of Peppermint, min. iii, in 1 oz. of Glycerin). Penicillin Lozenges or Gelatin Pastilles, containing an antiseptic and astringent, e.g. Thymol, Eucalyptus, or Menthol, with Krameria or Tannic Acid, or tablets, containing Potassium Chlorate, Borax and Cocaine, also afford considerable relief from the inflammatory pain. A linseed poultice or Cataplasma Kaolini, applied to the sides of the neck, is of value to relieve the pain. Sulphadiazine or Sulphadimidine orally, or Penicillin intramuscularly, will be advisable if the inflammation is severe. If suppuration occurs the abscess must be incised. In cases where the appearances are suggestive of diphtheria, antidiphtheritic serum should be given at the earliest possible moment and local treatment of the fauces, other than by saline gargles, withheld until the bacteriological report is received. In chronic tonsillitis and pharyngitis, the part may require to be painted with an active antiseptic, e.g. Silver Nitrate 1 per cent., or Iodine 1 per cent. in Glycerin, or with an astringent, a useful combination being Liquor Ferri Perchloridi, 60 min. in 1 oz. of Glycerin, of which the patient is instructed to swallow half a teaspoonful slowly. Antiseptic or astringent lozenges or pastilles are worthy of trial. Chronically infected tonsils which fail to respond to antiseptic treatment may require removal together with hypertrophied adenoid tissue in the naso-pharynx.

Vincent's angina is often cured by Penicillin Lozenges or by painting locally with either Tincture of Iodine or a 5 to 10 per cent. solution of Neoarsphenamine, but Penicillin intramuscularly or, if this fails, Neoarsphenamine (0·45 G) intravenously may be necessary.

CHAPTER III

DIGESTION (continued)—THE STOMACH

PHARMACOLOGY

GASTRIC digestion is effected by the proteolytic enzyme, pepsin, which, when activated by 0·2 to 0·4 per cent. of hydrochloric acid, converts proteins into peptones; and by rennin, which in the presence of calcium salts curdles milk by converting caseinogen into insoluble calcium caseinate. The secretion of gastric juice is normally regulated (*a*) through the secretory vagal endings which may be excited reflexly through the medulla by the taste and smell of food (psychic or appetite secretion), and (*b*) by a secretagogue substance, *gastrin*, which is formed in the pyloric mucosa in response to the presence of meat extracts and dextrin; gastrin, which is probably related to histamine and conveyed by the blood, induces both increased secretion from the gastric glands and also dilatation of the vessels. It should, however, be remembered that the reflex gastric secretion is also influenced by the higher psychical centres; pleasant emotions such as are promoted by congenial company and surroundings improve the appetite secretion, whereas emotions such as grief, anxiety, etc., may inhibit both the salivary and gastric secretions.

1. **Food.**—We have complete control over food and drink; these may be withheld for a time in order to rest the stomach, necessary fluid and Dextrose being given by intravenous injection or by enema; the activity of the gastric glands may be reduced by restricting the proteins or supplying them in peptonized form, and also by increasing the fat in the diet; conversely, the gastric secretion may be augmented by more appetizing food, by the use of condiments, by fruit juices, by soups containing meat extractives, or by additional protein.

2. **Drugs influencing Gastric Secretion.**—*The Drugs which increase gastric secretion* may be grouped thus: (*a*) *Gustatory Stimulants*, which act reflexly by stimulating the taste buds, e.g. the administration of simple bitters such as Quassia, Calumba, Quinine or Strychnine; aromatic bitters, e.g. Gentian or Orange;

flavours, e.g. Peppermint; pungents, e.g. Mustard; or Alcohol in the form of bitter or aromatic beverages. Drugs which increase gastric secretions by this psychic reflex should be administered shortly before meals: the bitters are particularly suitable for this purpose because after excitation of the taste buds by the unusual bitter taste, there follows a further augmentation of the gastric secretion in response to the pleasant taste of subsequent food. But it should be noted that artificial stimulants of the psychic reflex have little influence if the reflex be normal and they should not be continued after the normal response is restored lest the sensitiveness of the taste buds be decreased.

(*b*) *Chemical Stimulants.*—Egg albumin, meat, meat extracts, milk and bread augment the quantity and digestive quality of the gastric juice; water and salt solutions stimulate the secretion slightly. Alkalis, particularly alkali carbonates, owing to their evolution of carbon dioxide, cause an increased secretion of gastric acid if they are given in doses to produce an alkalinity. Drugs which neutralize the acid and leave a neutral solution, e.g. Magnesium Trisilicate, Tribasic Magnesium or Calcium Phosphates and Aluminium Hydroxide, do not have this secondary action. Histamine Acid Phosphate given by subcutaneous injection in dose of 0·001 G (1/60 gr.) causes a profuse flow of gastric juice. Alcohol in solutions of less than 10 per cent. strength also increases gastric secretion.

(*c*) *Nervous Stimulants.*—As the secretory nerve to the gastric glands is the vagus, drugs which stimulate the parasympathetic system will increase gastric secretion; therefore, owing to ganglionic stimulation, increased gastric acidity is associated with excessive tobacco smoking and, by exciting the vagal nerve endings, Physostigmine and Pilocarpine augment the flow of gastric juice although they are not used for this purpose in therapeutics.

Drugs which decrease gastric secretion may be grouped similarly: (*a*) *Reflex Depressants.*—Insipid and unpalatable foods, because of their unwelcome taste, will lessen the gastric secretions. Mucilaginous materials, by coating the taste buds in the mouth, and the frequent use of strong condiments, by lessening the sensitiveness of taste, will also interfere with the normal gustatory reflex.

(*b*) *Chemical Depressants.*—Fixed oils or fats, including cream, decrease the secretion of gastric juice but not sufficiently to counteract a hyperacidity. Strong alcoholic liquors reduce the secretion of gastric juice but, by irritation, augment the secretion of mucus. Pentamethonium and Hexamethonium inhibit gastric secretion.

(*c*) *Nervous Depressants.*—Atropine, Hyoscyamine and Hyoscine, and the drugs containing these anti-cholinergic alkaloids, by antagonizing the secretory vagal endings, diminish the secretion of both the acid and enzymes in the gastric juice or may completely inhibit the secretion.

3. **Drugs influencing the Acidity of the Gastric Juice.**—(*a*) *Hypochlorhydria.* When the gastric juice is deficient in acid as occurs in achylia gastrica, pernicious anæmia, rheumatoid arthritis, and carcinoma, Dilute Hydrochloric Acid, 60 to 120 min. in a tumblerful of water sipped through a tube during and shortly after meals, is the natural method of supplying the defect, but as the administration of acid tends to inhibit the secretion of Pepsin, this may have to be given simultaneously. Minor degrees of hypochlorhydria may be remedied by the use of some of the secretory stimulants discussed previously.

(*b*) *Hyperchlorhydria*, or increased acidity of the gastric contents, which may occur in gastric or duodenal ulcer or be associated with chronic dyspepsia, can be counteracted by the administration of alkalis. The **direct antacids** most suitable are:—Sodium Bicarbonate, Calcium Hydroxide or Carbonate, Magnesium Carbonates, Oxides or Hydroxide and Bismuth Carbonate; but two points must be remembered, first, that the carbon dioxide evolved from carbonates will excite later a further secretion of acid, and second, that the neutralizing values of these salts differ. The most effective is Magnesium Oxide; Magnesium and Calcium Carbonates have about half its neutralizing power, Sodium Bicarbonate only a quarter, while Bismuth Carbonate is only a very weak antacid. Administration of direct antacids forms the basis of Sippy's and other methods of treating gastric and duodenal ulcer (*see* p. 483). It should be noted, however, that excess of alkali will not only delay peptic digestion, but may lead to alkalosis. Hyperchlorhydria can also be reduced by those drugs which diminish the gastric excretion, namely by oils and fats, such as milk or cream, and by parasympathetic depressants, such as Atropine.

Magnesium Trisilicate and Aluminium Hydroxide are superior to the alkali antacids because they have the property of buffering the acid gastric contents. They do not allow the reaction to become alkaline as occurs from giving excess of alkali, thus they obviate a secondary secretion of acid and also an alkalosis.

4. **Drugs influencing Gastric Movements.**—The peristaltic movements of the normal stomach start at the cardiac end and finish at the antrum of the pylorus where independent rhythmical movements occur. Gastric peristalsis is stimulated by the vagus and inhibited by the sympathetic nerve; but the sympathetic supplies motor fibres to both the cardiac and pyloric sphincters. The acidity of the gastric contents does not influence the pyloric sphincter as was once believed. It appears that, although immediately after a meal the pyloric sphincter is closed, it begins five to ten minutes later to relax automatically in front of a wave of contraction in the pyloric antrum into which food has been driven by an increase in the tone of the cardiac portion. Still later the pylorus seems to remain relaxed even during the intervals between waves of contraction; from this fact it is apparent that duodenal regurgitation into the stomach can occur, provided the duodenal pressure is higher than that of the stomach, or if duodenal antiperistalsis occurs. The irritation of a duodenal ulcer by the gastric acid has been found to lead to the spasmodic closure of the pylorus.

Drugs increasing Gastric Movements.—Such drugs are of minor therapeutic importance. Stimulants of (*a*) the vagus centre, e.g. Digitalis; (*b*) the vagal ganglia, e.g. Nicotine, at first; (*c*) the vagal endings, e.g. Physostigmine and Pilocarpine, or (*d*) gastric irritants, can increase the movement of the stomach and may excite feelings of nausea. Those which act through the vagus also increase the tone of the gastric muscle.

Drugs diminishing Gastric Movements.—These have an important therapeutic value because some of them may be used appropriately as **gastric sedatives**. They may be classified thus: (*a*) *Central Depressants:* under the influence of General Anæsthetics, gastric movements cease and this effect is important for the surgeon; (*b*) *Depressants of the Vagal Ganglia*, e.g. Nicotine, late action; (*c*) *Depressants of the Vagal Endings*, namely Atropine and its related drugs, which are effective especially in diminishing spasmodic contractions or tone without interfering with the normal rhythmic movements; (*d*) *Stimulants of the Sympathetic Endings*, namely Ephedrine and Adrenaline, which check gastric contractions, but the action of Adrenaline is too brief to be therapeutically useful; (*e*) *Depressants of the Sensory Endings*, such as Cocaine, Chlorbutol, Dilute Hydrocyanic Acid or Chloroform, which diminish the reflex movements of the organ by anæsthetizing the mucous membrane; (*f*) *Morphine* has a characteristic action in causing relaxation and quiescence of the cardiac portion while it contracts the pylorus, and thus it delays the emptying of the stomach; (*g*) *Mechanical Protectives*—Light Kaolin and the insoluble salts of Bismuth, Magnesium and Calcium given before meals may reduce the gastric movements by forming a protective coating upon the walls.

5. **Carminatives.**—These drugs aid expulsion of gaseous accumulations which frequently cause discomfort by distending the stomach or give rise to painful spasmodic contractions of the viscus. Gastric flatulence from air swallowing is painless but that associated with an acute gastritis is painful and can be relieved by carminatives. The most effective carminatives are the volatile oils, particularly Oleum Anethi, Menthæ Piperitæ, or Cinnamomi, and the pungents, e.g. Ginger and Mustard. These diminish gastric movements, inhibit spasmodic contractions and reduce the tone of the cardiac sphincter and thus relieve the discomfort and permit egress for the gas.

Drugs which irritate the gastric mucosa in a moderate degree, such as Ammonium Bicarbonate and strong Alcohol, induce, reflexly through the medulla, temporary effects of a general stimulant character, such as acceleration of respiration, rise of blood-pressure and improvement of cardiac efficiency.

6. **Emetics.**—Vomiting is an intricate reflex act controlled by a centre in the medulla which may be excited by unpleasant or irritant sensations, derived usually from the fauces, stomach or abdominal viscera. The vomiting centre reflects these afferent sensations as efferent impulses through the vagus to the stomach, through the phrenic nerve to the diaphragm and by the intercostal nerves to the abdominal muscles. Preceding the act of vomiting, there is a period of nausea during which, as a result of gastric or other irritation, there occurs reflex stimulation of the salivary and bronchial secretions, and often also of the sweat. Before emesis occurs, a deep inspiration is taken, the glottis then closes and the stomach is compressed against the fixed diaphragm by the contractions of the abdominal muscles; the cardiac sphincter is then relaxed so that the gastric contents can be ejected. After emesis, there is a powerful expiratory effort; this, in infants, is sometimes valuable to remove tenacious bronchial secretions which have been rendered more fluid during the period of nausea.

Emetics act in two ways:

(*a*) *Reflex Emetics.*—These are drugs which produce powerful stimulation of sensory nerve endings—chiefly of the vagus in the stomach—and reflexly excite the vomiting centre in the medulla.

Irritation of the fauces by a feather or the finger is a familiar reflex excitant of vomiting. Indigestible food, excessive alcohol and many nauseous or irritant drugs, e.g. Digitalis, if given insufficiently diluted, can excite vomiting reflexly. Any drug which is employed as a reflex emetic should be prescribed as a draught and the patient directed to take repeated sips from this until vomiting results.

The reflex emetics available in the household as emergency measures are Sodium Chloride, a tablespoonful in a tumblerful of warm water, and Mustard, a teaspoonful in a cupful of water. The latter is usually more prompt in action and causes neither much circulatory nor nervous depression. Ammonium Bicarbonate, 0·6 to 2 G. (10 to 30 gr.), is rapid in action and causes little depression. The metallic salts, Zinc Sulphate, 0·6 to 2 G (10 to 30 gr.), and Copper Sulphate, 0·3 to 0·6 G (5 to 10 gr.) given in a cupful of water, are usually prompt emetics but unreliable in action; therefore, as they cannot be left in the stomach, they may require to be removed by the stomach tube; Zinc Sulphate is useful for lead poisoning and Copper Sulphate in yellow phosphorus poisoning to form the insoluble Copper Phosphide. Antimonii et Potassii Tartras and Antimonii et Sodii Tartras, 30 to 60 mg (1/2 to 1 gr.) both produce a prolonged and depressing nausea, and often repeated vomiting which may exhaust the patient. Ipecacuanha, usually prescribed as the Extractum Ipecacuanhæ Liquidum, 0·6 to 2 Mils (10 to 30 min.) or as the Tinctura Ipecacuanhæ, 15 to 30 Mils (1/2 to 1 fl. oz.), also acts slowly and produces in from 10 to 30 minutes vomiting which is preceded by considerable nausea and nervous depression; this drug is, therefore, not useful in acute poisoning but is quite suitable for the removal of indigestible food or, in infants, to assist the removal of thick bronchial secretion.

It has been suggested that Antimony and Ipecacuanha have also a central action: this is disproved by the facts that they act more quickly when given by mouth than when injected, and that, if they have been injected, the first vomit always contains some of the drug, showing that its excretion into the stomach has provoked the vomiting.

(*b*) *Central Emetics.*—The most important of these is Apomorphine Hydrochloride, 2 to 8 mg (1/32 to 1/8 gr.); this is a direct stimulant of the vomiting centre in the medulla and produces emesis whether given by mouth or hypodermically. The hypodermic Injection, 3 mg (1/20 gr.) in 1 Mil (15 min.), induces, usually within five minutes, vomiting which may be repeated until the stomach is emptied and then generally ceases. Apomorphine is the most valuable emetic in most forms of acute poisoning, but it may fail to act in narcotic poisoning if the medulla be already depressed; its action is accompanied by the usual symptoms of nausea but its depressant effects are comparatively slight.

Stimulation of the vomiting centre is also produced by large doses of Digitalis.

7. **Anti-Emetics.**—Drugs which relieve vomiting may act (*a*) by depressing the cerebrum, e.g. Hyoscine, Morphine, Bromides and hypnotics such as Chlorbutol; (*b*) by depressing the vagal endings, e.g. Hyoscine and Atropine; (*c*) by a local anæsthetic action on the mucosa, e.g. Cocaine, Chlorbutol, Dilute Hydrocyanic Acid, Phenol or Chloroform Water; and (*d*) by mechanical protection of the mucosa, such as the insoluble salts of Bismuth and Kaolin. Hyoscine 0·6 mg (1/100 gr.) or Chlorbutol is used to treat sea-sickness, which appears to be relieved also by Anthisan and by Dramamine in 100 mg (1½ gr.) doses.

8. **Drugs influencing Gastric Circulation.**—A modification of the circulation in the gastric mucous membrane is of minor importance, except in so far as it may increase the secretions, because the gastric mucosa has absorbent functions only in respect of volatile substances.

The *circulation can be increased* by many drugs which stimulate the sensory endings locally and induce reflexly a dilatation of the vessels which rouses a sense of warmth in the epigastrium. These drugs are Alcohol, Ether, Chloroform, volatile oils and pungents.

The *circulation may be diminished* and the secretions—especially of mucus—reduced by the astringents, e.g. Lead Acetate and Tannic Acid; or by sympathetic stimulants—Adrenaline and Ephedrine—which excite the vaso-constrictor endings.

9. **Gastric Hæmostatics.**—The drugs used to arrest gastric hæmorrhage are (*a*) astringents, e.g. Lead Acetate and Tannic Acid; and (*b*) sympathetic stimulants, e.g. Adrenaline and Ephedrine; they are rarely effective. Morphine is of great value because it allays the anxious restlessness of the patient and diminishes gastric movement and thus promotes a quiescent state of the organ which favours coagulation; it is not a direct hæmostatic. Blood transfusion, given slowly to avoid raising the blood-pressure, may be necessary.

THERAPEUTICS

Disorders of the stomach are among the commonest conditions which require treatment in medical practice. The majority are chronic in character and unassociated with any gross structural change in the stomach wall. The term "dyspepsia" is applied to these derangements, which may be either a subacute gastritis or a nervous dyspepsia.

In all forms of **dyspepsia,** there are certain ætiological factors which demand correction. It will frequently be found that the stomach has been subjected to gross abuse. Thus, meals may have been taken at very irregular intervals or the quality of the food may have been unsatisfactory. The patient may have been over-worked or be living in a state of nervous unrest. Again, mastication may have been imperfect because meals were eaten too hurriedly or because the teeth were defective or dentures ill-fitting. Meals should be taken at regular hours and should never be hurried; if they cannot be taken in company, the patient may be advised to read a book so that the temptation to eat too quickly may be avoided. A period of rest for half an hour or more after the principal meals is desirable but a moderate amount of physical exercise must be insisted upon between meals. The majority of dyspeptic subjects are constipated, therefore an adequate daily evacuation of the bowels must be ensured.

The dyspepsias may be grouped into two general types: in the first, the motor and secretory functions of the stomach are decreased; whilst in the second, the converse conditions of hypermotility and hyper-secretion prevail. The terms "atonic" and "hypertonic" dyspepsia will be applied respectively to these two types, which for effective treatment require different therapeutic procedures.

In **atonic dyspepsia**, the stomach tends to be dilated, its motility is diminished and the secretion of hydrochloric acid is reduced. In this condition meals should be small in bulk and easily digested; they should be composed of materials which compel mastication, therefore soft foods are highly undesirable. The diet should consist largely of protein on account of its action in stimulating the flow of gastric juice, and carbohydrates should be represented mainly by cereals, whilst vegetables and fruits which contain much cellulose must be forbidden. Fats should also be omitted on account of their inhibitory effect on gastric secretion. Condiments and sauces are useful in moderation. In order to avoid distension of the stomach, fluids should not be taken with meals but only in the intervals between them. It is well to advise the patient to lie, while resting after a meal, on the right side so that emptying of the stomach may be favoured.

Of the drugs employed in atonic dyspepsia the **bitters** are probably the most useful. Calumba and Quassia, given before meals, either as the Tinctures or Infusions, and other members of this group, improve the appetite and reflexly increase the gastric secretion. Nux Vomica, usually prescribed as the Tincture, is particularly valuable since, in addition to its bitter taste, it increases the motor activity of the stomach by its action on synapses. The bitter taste of such purgatives as Rhubarb and Cascara makes them particularly serviceable in dyspepsia when constipation is present. The aromatic bitters, such as Gentian, help to relieve flatulence, which is a frequent symptom; this may also be treated by incorporating a carminative, such as a preparation of Ginger, Cardamom or Peppermint, in the prescription. Sodium Bicarbonate in doses of 10 gr. acts as an alkaline stomachic and dissolves mucus; the immediate neutralization of acid which it effects is commonly followed by a secondary secretion of acid—a useful sequence in atonic dyspepsia where the production of acid is subnormal. Hypochlorhydria may be further corrected by giving Acidum Hydrochloricum Dilutum with water. Finally, abdominal massage is of service to increase the tone of the abdominal muscles and raise the intra-abdominal pressure; dilatation of the stomach is thus prevented and the viscus enabled to empty itself more rapidly.

Chronic gastritis, e.g. of alcoholism, is treated upon the principles laid down for atonic dyspepsia. An excessive secretion of gastric mucus is one of its most troublesome symptoms; this may be treated by daily gastric lavage with 5 per cent. Sodium Bicarbonate solution or by the use of alkaline mixtures by mouth. If, however, there is achlorhydria, the administration of Dilute Hydrochloric Acid is clearly indicated.

Hypertonic dyspepsia is characterized by an increased motility of the stomach and increased secretion of hydrochloric acid. Spasmodic contraction is often present at the pylorus and in other situations; and peptic ulcers tend to develop. The appropriate treatment must, therefore, aim at diminishing the secretion and neutralizing its excess of acid. Diet is of primary importance. Proteins must be chosen with care, because, although they exert a buffering effect on the acid secretion, many contain purin bodies and extractives which stimulate the secretion of the gastric glands. The proteins of milk are practically free from this defect; milk will neutralize its own bulk of gastric juice and it is, therefore, of great value in the treatment of severe cases of hypertonic dyspepsia. Protein may also be given in the form of eggs, steamed fish and chicken. Tough meat, over-cooked or twice-cooked meat, salted meat or fish, and "made-up" dishes should be avoided. Carbohydrates should be taken chiefly in the form of cereal foods, and heavy carbohydrate foods, such as potatoes and bread, must be curtailed. New potatoes and fresh bread are eliminated. Fruits and vegetables, which leave a considerable indigestible residue, are forbidden. Fats may be taken liberally with advantage as they decrease the secretion of gastric juice; therefore, cream may be added to the milk or Oleum Olivæ given before meals. Subsidiary articles of diet containing purin bodies and other extractives should be either interdicted or curtailed; soups, meat extracts, tea, coffee and cocoa belong to this category. Condiments, sauces, vinegar and alcoholic or aerated drinks are likewise forbidden and smoking reduced to a minimum.

Of the drugs used in hypertonic dyspepsia, **alkalis** are the most important, the relief of symptoms which they afford being dependent on the neutralization of the excessive acid in the stomach. Subsequent secretion of hydrochloric acid is least when neutralization takes place gradually and when no carbon dioxide is evolved; for these reasons, insoluble alkalis, e.g. Magnesium Oxide, Mistura Magnesii Hydroxidi, and to a lesser extent the Carbonates of Magnesium or Calcium, are preferable to a soluble alkali such as Sodium Bicarbonate; moreover, Sodium Bicarbonate in large doses may cause a systemic alkalosis. Alkalosis is avoidable by using the buffering agents, namely Magnesium Trisilicate or Aluminium Hydroxide. Bismuth Carbonate, although it has little neutralizing power, is often given in combination with other alkalis to form a protective coating on the gastric mucous membrane but this effect is of doubtful value.

Atropine is also a useful drug in hyperchlorhydria and is best prescribed in the form of Tinctura Belladonnæ or Atropinæ Sulphas before meals or at night; owing to its paralysing action on the vagal nerve endings, it decreases the motility of the stomach and relieves spasm, and as the secretory nerve endings are also depressed, gastric secretion is reduced or inhibited, and thus hyperchlorhydria is prevented.

In **organic diseases** of the stomach, a dyspepsia conforming approximately to one or other of the above types is invariably present.

Peptic ulceration, whether gastric, pyloric or duodenal, is treated upon the lines indicated for hypertonic dyspepsia. The patient is kept in bed and placed on a strict *régime* in which the nature, quantity and times of the feeds and of the administration of the drugs ordered are laid down strictly. A widely used method of treatment is that introduced by Sippy and modified by Hurst. The object of this *régime* is to keep the gastric juice as far as possible continuously neutralized. Feeds consisting of 5 to 7 fl. oz. of milk containing 0·6 G (10 gr.) of Sodium Citrate and 4 to 8 Mils (1 to 2 fl. dr.) of Mistura Magnesii Hydroxidi are given at two-hourly intervals during the day. The patient receives also before the feeds alternately half an ounce of Olive Oil and 0·3 mg (1/200 gr.) of Atropine Sulphate. Tribasic Magnesium or Calcium Phosphate in doses of 4 G (60 gr.) is given in the early morning, after the afternoon feeds, and before retiring to sleep. Magnesium Trisilicate and Aluminium Hydroxide resemble these salts in obviating alkalosis and a secondary acid secretion. When there is pyloric spasm with consequent accumulation of gastric juice, the stomach may be emptied by a Senoran's evacuator, immediately before the last powder is given. Atropine Sulphate, 0·6 mg (1/100 gr.) will serve to inhibit secretion of gastric juice during the night. This treatment, after a few days, commonly gives complete relief from the symptoms, but the diet must be maintained without modification for at least three weeks after pain has ceased. The monotony of the milk diet may, however, be relieved by flavouring it with tea or coffee and by substituting at intervals junket, custard or vegetable *purées*. A normal but curtailed dietary is resumed gradually and the patient kept under close supervision for some time; any evidence of recurrence requires a temporary return to the strict diet.

Hæmatemesis, or the vomiting of blood, occurs as the result of bleeding, usually from ulcer or carcinoma, from the walls of the stomach, œsophagus or duodenum, and it is often accompanied by the passage of black stools (melæna) containing digested blood. The treatment of gastric or duodenal hæmorrhage consists in reassuring the patient and *ensuring quietude*. Anxiety and restlessness may be allayed by injecting Morphine Hydrochloride 16 mg (1/4 gr.), which will also check peristalsis. The administration by mouth of *hæmostatics*, such as Liquor Adrenalinæ Hydrochloridi, or Tannic Acid, or the injection of drugs regarded as increasing the coagulability of the blood, such as Calcium Gluconate, may be tried, but these remedies are not very reliable; in the majority of cases bleeding ceases spontaneously. Even when hæmorrhage has ceased, no food or liquid should be given by mouth for a day, the patient being allowed only mouth washes; food may then be cautiously permitted and, if tolerated, the calorific value of the diet is increased as rapidly as possible. A high protein diet suitable for the debility and anæmia following hæmorrhage has yielded good results; the Lenhartz diet, which contains milk, eggs and raw meat, is a typical example of such a *régime*. The Meulengracht diet, likewise advised after hæmorrhage from a peptic ulcer, consists of ordinary nourishing foods given in a state of fine subdivision. Iron should be given in full doses and in a non-irritant form during convalescence, e.g. Ferri et Ammonii Citras may be given by mouth in doses of 30 gr. four times daily. If the hæmorrhage has been severe, blood transfusion may be given, but only slowly as, by raising the blood-pressure, it may prolong bleeding. In grave cases, the risk of an operation to arrest the bleeding should be carefully weighed.

Achlorhydria, which is associated with pernicious anæmia, chronic (usually alcoholic) gastritis, rheumatoid arthritis, gastric carcinoma, and chronic diarrhœa, is treated by administering to the patient Dilute Hydrochloric Acid in the form of lemonade of the same strength as that of the normal gastric juice. The drink should best be sucked through a tube so as to prevent the acid from attacking the teeth.

Acute gastritis, which is often accompanied or followed by acute enteritis and colitis, usually occurs as the result of the ingestion of an irritant, e.g. unsound food, or a surfeit of food or alcohol. The stomach may expel its contents spontaneously or an emetic may be necessary; in either event, it is advantageous to wash out the last traces of the irritant from the viscus and to administer Castor Oil so as to evacuate the intestine. Food should be withheld for 24 hours but sips of water may be permitted; after this period, feeding is cautiously recommenced with diluted milk, which is augmented by other foods in accordance with the tolerance of the patient. In severe forms of acute gastro-enteritis, treatment designed to avert shock and dehydration is of primary importance.

Vomiting.—Vomiting is a symptom in many diseases of the stomach but, because of the many afferent impulses which can excite the vomiting centre, it is almost as frequently due to some cause operating outside the stomach. Vomiting is, therefore, a prominent symptom in such diverse conditions as uræmia, ketosis, acute infectious fevers, pregnancy, appendicitis, peritonitis, intestinal obstruction, disturbances of the semicircular canals, migraine, increased intracranial tension, tabes dorsalis and hysteria. The need for a thorough investigation of the cause before deciding the treatment will now be apparent.

When vomiting has once commenced it tends to persist, as the reflex is aroused by comparatively trifling stimuli long after the original exciting cause has ceased to operate. Repeated vomiting is followed in the course of a day or two by the development of starvation ketosis and, if it persists longer, a dangerous state of alkalosis, associated with tetany, may arise, due to the loss of chloride ion in the vomit and, moreover, the patient may also become seriously dehydrated.

When the cause of the vomiting, so far as is practicable, has been appropriately removed, suitable treatment can be prescribed. If it arises from the ingestion of irritant material or from the excretion of toxic products into the organ, the stomach should be washed out with the aid of a stomach tube. Alternatively, the patient may be encouraged to take large draughts of warm water containing 2½ to 5 per cent. of Sodium Bicarbonate; these will subsequently be vomited and by this means the stomach is washed out almost as effectively as by direct lavage. One or more of the various gastric sedatives should then be administered until relief is secured. The most suitable are Light Kaolin or Bismuth Carbonate every four hours as a powder or suspension with mucilage, and Chlorbutol in doses of 5 gr. at two-hourly intervals; the last-named drug is specially valuable in sea-sickness. Only the blandest forms of nourishment should be given when sickness subsides. Two or three fluid ounces of Normal Saline at two-hourly intervals may be followed by similar amounts of albumin water and then by whey, milk and soda, or diluted milk (milk, 2 fl. oz., water, 2 fl. oz., Sodium Citrate, 5 gr.). Later the milk may be thickened by arrowroot and broths may be given.

If the vomiting is persistent and resists treatment, loss of fluid from the tissues should be replaced by giving intravenously or per rectum 1 to 2 pints of Injection of Sodium Chloride containing 5 to 10 per cent. Dextrose, and it is important to give fluid liberally in order that toxic substances may be eliminated by the kidney. The appearance of acetone bodies in the urine is a signal for giving Injection of Sodium Bicarbonate intravenously, if the stomach will not tolerate the salt. The Compound Injection of Sodium Lactate may be used in preference. If Dextrose is being given, 5 Units or more of Insulin may be injected twice daily to aid the metabolism of fat. Food constituents, other than Dextrose, salts, and Alcohol, are not absorbed by the rectal mucosa; and predigested nutrient enemata are now known to be of little value in aiding nutrition. In the protracted vomiting of unrelieved intestinal obstruction, the patient may ultimately develop alkalosis from excessive loss of chloride and the carpopedal spasms of tetany may appear; these can be relieved by injecting Normal Saline rectally or, if severe, intravenously, or Injection of Calcium Gluconate may be given. Hiccough, which frequently accompanies vomiting, is relieved by Morphine with Atropine, by inhaling CO_2 or small doses of Amyl Nitrite.

Vomiting due to cerebral tumour or meningitis is relieved by intravenous injections of 50 Mils of 50 per cent. Dextrose solution, which reduces intracranial pressure.

Sea-sickness may be prevented or relieved by Hyoscine Hydrobromide 0·6 mg (1/100 gr.) or by Chlorbutol 0·6 G (10 gr.). Anthisan 100 mg (1½ gr.) and Dramamine (β-dimethylaminoethylbenzohydrylether-8-chlorotheophyllinate) 100 mg (1½ gr.) have also proved effective.

Emetics.—Apart from the treatment of acute poisoning, vomiting is now rarely employed as a therapeutic procedure. Emetics are sometimes used for infants with capillary bronchitis or broncho-pneumonia, as their cough reflex is less sensitive than that of the adult. If vomiting is induced by Tinctura Ipecacuanhæ, the stomach and the bronchial tubes are emptied simultaneously. In acute œdema of the lungs arising from inhalation of irritant gases, similar treatment is useful.

In **inoperable cancer** of the stomach, lavage often gives considerable, although temporary, relief. Dilute Hydrochloric Acid may be required for the achlorhydria and Pepsin may be advisable with it to assist protein digestion.

In the later stages of carcinoma, the administration of Morphine for the relief of pain has to be repeated frequently; Pethidine and Disephonine may be tried as substitutes; the use of a dilute solution of Cocaine to anæsthetize the gastric mucous membrane before meals may enable food to be retained.

CHAPTER IV

THE DUODENUM AND INTESTINE

PHARMACOLOGY

THE pancreatic juice which enters the duodenum contains *sodium carbonate* in amounts capable of neutralizing an equal volume of gastric juice; and three enzymes—*trypsin*, which splits proteins into polypeptides and then into amino-acids; *amylase*, converting starch into maltose; and *lipase*, which converts fats into glycerol and fatty acids. Bile assists in digesting fats because the *bile salts* form a co-enzyme for lipase; it also promotes the absorption of fats by lowering surface tension and dissolving fatty acids. Bile also precipitates unpeptonized protein, diminishes intestinal putrefaction and accelerates peristalsis. The succus entericus contains three *invert ferments* which convert disaccharide sugars into glucose; *erepsin*, which completes the breakdown of proteins into amino-acids; *enterokinase*, the activator of trypsinogen; and *lipase*.

The secretions of the pancreas and the intestinal juices are controlled by the vagus, which augments the secretions and their enzymes, and by the sympathetic which inhibits them; in addition, the acid from the stomach in association with sodium cholate from the bile converts the prosecretin of the intestinal mucosa into *secretin* which, by way of the blood, increases the water and alkali in the pancreatic secretion. In the intestine, the food also comes in contact with intestinal bacteria, which convert carbohydrates into lactic, butyric and carbonic acid, cellulose into gaseous methane and carbon dioxide, proteins into phenols, amino-acids into amines, e.g. histamine, etc. Owing to bacterial activity, the intestinal reaction again becomes acid but it reverts to alkaline in the lower bowel owing to the presence of ammonia-forming organisms.

The food may have to be regulated in order to reduce the activity of the pancreas and liver; then a choice of foods containing a minimum of lipoid and fat is indicated and the selection of those carbohydrates which are easily converted to glucose. If intestinal inflammation be present, food must also be restricted and be of a character which will not excite excessive acidity in the stomach nor irritate the duodenum; therefore milk, cream and egg albumin are permissible but, so as to ensure a low acidity of the gastric contents, it is usually necessary to administer also antacids, e.g. Magnesium Oxide, Hydroxide, Trisilicate, or Carbonate, or Sodium Bicarbonate; and, in addition, Atropine. The character of the food also modifies biliary secretion; a high protein diet increases the secretion of bile salts, while carbohydrates lessen their formation. Fats promote the emptying of the gall bladder.

The **Pancreatic, Biliary and Intestinal secretions** are not very effectively within our control by pharmacological means. Food, as we have seen, modifies them to some extent and, if the presence of fat or undigested meat in the fæces suggests pancreatic insufficiency, a diet containing much carbohydrate, together with Casein Hydrolysate, is indicated. The administration of Pancreatin in enteric-coated capsules is not of much therapeutic value, nor is its oral use with large doses of Bicarbonate to prevent its destruction by the gastric acid more effective. Vagal stimulants of the secretions, e.g. Physostigmine or Pilocarpine, are indicated theoretically but in therapeutics they are not very helpful.

The drugs which diminish these secretions are of little practical value. Alkalis administered after meals decrease pancreatic secretion, and vagal depressants, such as Atropine, diminish both pancreatic and intestinal secretions but have no influence on the output of bile. Drugs which diminish the secretion of mucus will be considered under astringents.

Cholagogues.—These are drugs which increase the flow of bile. Many purgative drugs, e.g. Calomel, have been regarded as indirect cholagogues because they accelerate the passage of the intestinal contents so that insufficient time is afforded for the reduction of the bile pigments which therefore colour the fæces green. The term "indirect cholagogue" is better reserved for drugs which cause a flow of bile from the gall-bladder. Fats, particularly egg yolk, and to a lesser extent proteins, augment the expulsion of bile, probably through some absorbed product of their break-down which contracts the gall bladder; Olive and Castor Oils have this effect. The presence of a Hypertonic Saline Solution in the duodenum also contracts the gall bladder and Magnesium Sulphate in 33 per cent. solution is given orally for this purpose. Adrenaline by sympathetic stimulation contracts the gall bladder.

The only true cholagogues are the bile acids which augment the activity of the liver cells; Taurocholic Acid in doses of 8 G increases the flow for twenty-four hours; Glycocholic Acid is less effective. Salicylates and Extractum Fellis Bovini have a slight action. Bile salts aid absorption of Vitamins D and K.

Intestinal Absorption.—The absorption of the products of gastric and pancreatic digestion commences in the duodenum but takes place chiefly in the jejunum and ileum. The absorption is partly an osmosis but mainly a selective function of the epithelium. Proteins are absorbed as amino-acids, carbohydrates as monosaccharides, and fats as glycerol and soaps of fatty acids. The rate of absorption depends upon the vascularity of the absorbing mucosa, on the osmotic tension of the intestinal contents and on the speed of their transmission.

There are no satisfactory means of accelerating absorption by the bowel except by altering the diet and ensuring its efficient digestion. It is probable that Volatile Oils, Pungents, Alcohol and other drugs which act as mild irritants to the mucosa increase its vascularity and thus accelerate absorption, but little practical use is made of this.

Absorption will be retarded or prevented by the use of purgatives, particularly by those which accelerate peristalsis in the small intestine and by saline purgatives. Astringent drugs, by precipitating the proteins in the food and in the superficial cells of the villi, retard absorption of proteins but this effect has no therapeutic value.

Insoluble powders, such as Light Kaolin, Bismuth Carbonate, and Powdered Charcoal, besides having a protective effect on the mucosa, will hinder the absorption of toxins formed by bacterial action; the fine particles adsorb not only bacterial toxins but to some extent also bacteria, and for this reason they have a value in cholera and other intestinal infections.

Transmission of the Intestinal Contents.—Purgatives.—The automatic movements of the intestinal muscle are partly churning and partly progressive. They are regulated reflexly by Auerbach's plexus; and controlled by the vagus, stimulation of which augments the contractions and tone of intestinal muscle, and by the sympathetic which, when stimulated, inhibits the contractions and lowers tone; the sympathetic is, however, the motor nerve to the ileo-cæcal sphincter and regulates its tone. The propulsion of a bolus results from a co-ordinated reflex involving relaxation in front of and contraction behind the bolus. In the large intestine the propulsive mechanism is similar, but the nervus erigens has the functions of the vagus. Normally food reaches the ileo-cæcal sphincter in 3½ hours and is delayed there for an hour, by which time absorption of foodstuffs is complete; water is absorbed also from the colon. A meal has reached the hepatic flexure in 6 hours, the splenic flexure in 9 hours, the iliac colon in 12 hours and the pelvic colon in 18 hours. It should be noted that a meal, or even a moderate gastric irritant, e.g. a volatile oil, originates (*i*) a *gastro-iliac reflex* by which the contents of the lower ileum are rapidly transferred to the cæcum and also (*ii*) a *gastro-colic reflex* which excites in the colon a powerful wave of contraction so as to drive the contents onwards. In front of this the pelvi-rectal sphincter may become relaxed and the contents thus pass into the rectum when they arouse the *defæcation reflex*.

Purgatives or Aperients are drugs which facilitate or accelerate the evacuation of the bowel. They will be grouped in accordance with the potency of their action in ordinary dosage.

Laxatives.—Under this heading will be considered those measures or drugs which facilitate the action of the bowels and cause in 10 to 18 hours a soft motion without griping. Such an effect can be produced (*a*) by foods or drugs which leave in the intestine an insoluble residue and thus, by increasing the bulk of the intestinal contents, stimulate reflex peristalsis. A laxative diet may be ordered; this should contain oatmeal porridge, wholemeal bread, fresh vegetables and fruits, which leave a residue of cellulose. Similar physical stimulants of peristalsis are figs, prunes, tamarinds, Psyllium seeds, and Agar; (*b*) by drugs which lubricate the intestinal mucosa and contents, such as Liquid Paraffin and, less effective because they are soon absorbed, Olive and Almond Oils.

Saline Purgatives.—These are drugs which maintain the fluidity of the intestinal contents by preventing the normal absorption of water; they are soluble salts containing ions which are absorbed with difficulty by the intestinal mucosa. The Magnesium ion is least absorbed and Sodium less readily than Potassium; the anions in order of inabsorbability are the Sulphates, Phosphates, Tartrates and Citro-tartrates. Magnesium Sulphate is therefore the most active saline purgative; when given by mouth it does not increase the magnesium content of the blood and, when injected, it is not purgative; hence its action is clearly exerted within the alimentary canal.

Saline Purgatives act thus: (1) Because the salt is one which is not readily absorbed, therefore (2) it maintains the osmotic tension of the contents of the intestine, and thus (3) prevents the absorption of water; (4) the increased fluidity and bulk of the intestinal contents leads to augmented peristalsis and more rapid transmission of the contents into the colon. This responds to the bulky fluid mass by exhibiting more active contractions, so that evacuation soon occurs of a stool, first of normal consistency and then of a profuse watery character, containing 80 per cent. of the saline purgative. Salines should be given in dilute solution with a large bulk (a tumblerful) of water. Taken thus they prevent the absorption of the water given with them and produce within 1/2 to 2 hours a watery motion unaccompanied by griping but removing the bulk of the intestinal contents. They should, as a rule, be prescribed before breakfast on an empty stomach when the gastro-iliac and gastro-colic reflexes will also be excited by them.

If a saline purgative be given by mouth *in concentrated solution*, it forms in the intestine a hypertonic solution which not only prevents the absorption of water, but also actually draws water by osmosis into the intestine from the blood and surrounding tissues; thus it will cause a temporary increase in the erythrocyte count. When prescribed in this way saline purgatives may take 10 or more hours to act, but this principle should be employed when salines are desired to drain œdematous fluid from the tissues or to decrease intracranial tension.

The Salines in common use are: Magnesium and Sodium Sulphates, Sodium Phosphate, Sodium Potassium Tartrate (as Seidlitz Powder), Potassium Acid Tartrate and their preparations. A commonly used formula is Mistura Alba (B.P.C.): Magnesium Sulphate 60 gr., Light Magnesium Carbonate 10 gr., and Peppermint Water to 1/2 fl. oz.

Mild Irritant Purgatives.—These are drugs which produce a moderate irritation of the mucous membrane of the small intestine and thus excite reflexly, through Auerbach's plexus, an increased peristalsis and a more rapid transmission of the fluid contents into the colon. They produce usually in from 8 to 12 hours one or two soft, formed stools unaccompanied by griping. In this group we may place Castor Oil which, after it is hydrolyzed by lipase into irritant ricinoleates, acts upon the small intestine; but as its fatty esters are absorbed in the small bowel, Castor Oil does not irritate the colon nor cause pelvic congestion. Sulphur acts as a mild purgative because it is converted into alkali sulphides which are mild irritants.

Anthracene or Anthraquinone Purgatives.—These owe their activity to glycosides which are absorbed in the small intestine and hydrolyzed in the tissues into emodin or trihydroxymethylanthraquinone which carried through the circulation stimulates the colonic muscle directly. They increase colonic peristalsis and cause varying amounts of griping, colic and pelvic congestion. The members of the group are Cascara, Rhubarb, Aloes and Senna. With the exception of Rhubarb, which, owing to its Tannic Acid, has an astringent after-effect, they have the advantage that they can be given for long periods without inducing atony or tolerance, i.e. without necessitating increased dosage. They produce in from 6 to 10 hours soft stools with moderate griping. Phenolphthalein also acts mainly in the large intestine.

Hydragogue Purgatives or Cathartics.—To this group belong Ipomœa, Jalap, Colocynth and Podophyllum. These drugs contain glycosidal resins which in the alkaline intestine, by the aid of lipase and bile, are hydrolyzed with the liberation of irritant glycosides. Their action commences in the small intestine and continues throughout the bowel. Owing to their powerful irritant properties they greatly accelerate and augment peristalsis so that the fluid contents of the intestine are hurried rapidly into the colon, and discharged from there before adequate time has elapsed for their concentration by the absorption of water. Hydragogue purgatives produce within 2 to 6 hours, a copious watery stool which consists of the normal watery contents of the small intestine, and purgation is accompanied by considerable griping, colic and straining. The term "*drastic purgatives*" is applied to those which cause severe irritation and congestion of the intestinal mucosa, resulting in increased secretion of mucus, or even catarrh, and repeated liquid evacuations accompanied by colic and straining. Large doses of the glycosidal purgatives and Croton Oil (1/2 to 1 min.), which acts in about thirty minutes, will produce this.

Mercurial Purgatives.—All Mercury salts are purgative but the soluble salts, being easily absorbed, cannot be so used. From the insoluble preparations small amounts of soluble oxides and albuminates are formed, and these stimulate peristalsis in both the small and large intestine with the result that in 4 to 8 hours a soft bulky stool is evacuated, usually without much griping; after large doses, the action may be followed by several watery stools. The preparations used are Calomel, Pilula Hydrargyri and Hydrargyrum cum Creta, the last particularly for children. The mercurial purgatives have also an antiseptic action in the intestine.

Neuro-Muscular Stimulants, Hypodermic Purgatives.—The movements of the intestine can also be increased (1) *by drugs which stimulate the vagal receptors,* e.g. Physostigmine, Neostigmine, Carbachol or Pilocarpine; these excite powerful peristaltic movements and increased intestinal tone and secretions. Their action is associated with considerable griping and, as they have effects upon other organs also, e.g. the heart, they are rarely employed as purgatives in man. The Injection of Carbachol or of Physostigmine Salicylate is administered hypodermically to increase the tone and reflex excitability of the intestine in intestinal atony; (2) *by drugs which increase the reflex excitability of Auerbach's plexus,* namely Nux Vomica or Strychnine. With this object, Extractum Nucis Vomicæ is frequently added to purgative pills, but the student should note that Strychnine is not by itself a purgative, it merely increases the reflex responses of the intestine to the stimulation of a bolus; (3) *by direct stimulants of the involuntary muscle,* such as Injectio Pituitarii Posterioris. This, when given subcutaneously or intramuscularly, is a valuable means of increasing the rate and amplitude of the intestinal movements without greatly augmenting the tone; therefore it is often preferred to Carbachol or Physostigmine, or may be used in combination with one of these in treating paralytic ileus. In toxic dosage Lead salts and Digitalis also increase intestinal tone by a direct action on the plain muscle.

Intestinal Sedatives and Antispasmodics.—The drugs which exert a sedative action on the intestine may be classified thus: (1) *Mechanical Protectives.*—Light Kaolin, salts of Bismuth, and to a lesser extent the insoluble salts of Calcium may protect the intestinal wall from irritation by forming over the mucosa a physical coating and thus diminish peristalsis; they also adsorb bacteria and toxins; in full dosage they are given before meals to treat diarrhœa. Bismuth Carbonate and Salicylate, as well as Calcium Carbonate, are administered as powders or suspended with Mucilage of Tragacanth in mixture form, while Pulvis Cretæ Aromaticus, without or with Opium, is commonly prescribed for children. Both the Bismuth and Calcium Salts tend to be constipating, whereas the insoluble Magnesium Oxides and Carbonates, which are converted into Chlorides, will later have a saline purgative effect. (2) *Vagal Depressants.*—Atropine, Hyoscyamine and Hyoscine, which antagonize Acetylcholine and thus eliminate vagal action, lower intestinal tone and check spasmodic contractions without interfering with the normal peristaltic movements; they are, therefore, valuable to check griping or colicky pains and are given in association with drastic purgatives, e.g. Pilula Colocynthidis et Hyoscyami. In emergency Atropine Sulphate may be injected to relieve intestinal spasm or in less urgent cases Tincture of Belladonna or Extract of Hyoscyamus may be given by mouth. (3) *Sympathetic Stimulants*, e.g. Adrenaline, arrest for a brief period the intestinal movements but contract the sphincters; Ephedrine relaxes intestinal spasm and movement for an hour or more but has not proved of practical value. (4) *Muscular Tone.*—Morphine, by raising the tone of the intestinal muscle, diminishes the amplitude of peristalsis; this delays the transmission of the contents and induces constipation. This result is augmented by the action of Morphine in contracting the pyloric and ileo-cæcal sphincters. Codeine and Diamorphine have much less sedative influence upon the bowel than Morphine. (5) *Muscular Depressants.*—The important drugs which exert a direct depressant action on intestinal muscle are the Volatile Oils and Chloroform which, in the form of flavouring waters and spirits, have a value as *carminatives* in alleviating spasmodic intestinal contractions which originate griping pain. The carminatives most commonly used are the preparations of Mentha Piperita, Cinnamomum and Anethum, the last particularly for children. Papaverine and Pethidine also inhibit intestinal tone and contractions and are very effective means of allaying the pain of intestinal spasm.

Intestinal Astringents.—These act locally by precipitating the proteins in the superficial cells of the mucous membrane and thus they check mucous secretion and form on the mucosa a protective coating which lessens reflex peristalsis; they also precipitate the food proteins. These effects delay the transmission of the intestinal contents so that more time for absorption of water is allowed and, therefore, constipation results from their use. The intestinal astringents form two groups: the *metallic series*—Lead Acetate and the soluble salts of Iron, Silver, Alum and Copper; and the *tannic acid series*—Krameria, Catechu, and Kino. The crude vegetable drugs containing Tannic Acid are preferable to the pure acid, since the latter is soon neutralized in the duodenum, whereas the crude drugs are slowly disintegrated and liberate Tannic Acid even in the lower acid part of the intestine.

Intestinal Antiseptics.—The less absorbable Sulphonamides, Phthalylsulphathiazole, Succinylsulphathiazole and Sulphaguanidine, are the most active intestinal antiseptics. They are used effectively to treat bacillary dysentery and as prophylactics against infection by the gas-gangrene Clostridia and E. coli after colonic operations. They may so sterilize the intestinal contents that bacterial synthesis of Vitamin B is impaired. Emetine Hydrochloride, Carbarsone, Acetarsol and Chiniofon are specifics against amœbic dysentery; and Chloromycetin and Aureomycin are effective for typhoid fevers. Formerly Calomel, Bismuth Salicylate, Phenol, Salol, Betanaphthol, and Thymol were used but none of these was a satisfactory intestinal antiseptic.

Anthelmintics.—These drugs expel or kill worms. Vermifuges merely expel the parasites alive, while vermicides are toxic to them. Amongst vermifuges are included Santonin and hydragogue purgatives. The principal anthelmintics are: For *tapeworm*, Filix Mas, or Pelletierine Tannate; for *roundworm*, Santonin or Oleum Chenopodii; for *threadworm*, Gentian Violet, Diphenan, or Oil of Chenopodium orally, and Quassia, Hypertonic Saline, Chenopodium Oil or Turpentine solutions locally as enemas; for *hookworm* Oleum Chenopodii is most effective for ankylostoma duodenale, whereas Tetrachlorethylene, Carbon Tetrachloride or Thymol are advised for necator americanus; Hexylresorcinol is effective against most worms.

Enemata.—Some remedies may be administered by enema, that is, by injection, when warmed to body temperature, into the rectum.

(1) *Nutrient or Stimulant Enemata*, consisting of about 5 fl. oz. of fluid foods, such as beef tea, eggs, etc., peptonized or pancreatized foods, are of little value because only Glucose, salts, water and volatile substances are absorbed from the mucous membrane of the large intestine; traces of amino-acids, insufficient however to replace protein loss, are also absorbed. Nutrient suppositories have also little or no value. Enemas of Normal Saline, often with 5 per cent. Glucose added, in amounts of 15 to 20 fl. oz. are given slowly during about 30 minutes from a douche can in cases of severe hæmorrhage or collapse in order to restore the blood-volume; sometimes small amounts of alcoholic stimulants, well diluted, are added to them. (2) *Simple Evacuant Enemata*, such as warm water (68° to 70° F.) in amounts of 1 to 2 pints of water containing soap (1/2 oz. to 1 pint) which, by lowering surface tension, helps to break up hard fæcal masses, are valuable means of emptying the lower bowel rapidly. Olive Oil, Liquid Paraffin or

Glycerin (1/2 fl. oz.) are also injected as lubricants or stimulants to the rectal mucosa in order to excite defæcation. (3) *Anthelmintic Enemata.*—These are used to remove threadworms; examples are Hypertonic Saline (5 per cent.), Infusion of Quassia (5 per cent.), and Oil of Turpentine (1 per cent.), or Oil of Chenopodium (0·1 per cent.) in emulsion; or to remove amœbæ, e.g. Chiniofonum (2 per cent.). (4) *Astringent and Antiseptic Enemata.*—These consist of solutions of (0·02 to 0·2 per cent.) of Tannic Acid, Zinc Sulphate, or Silver Nitrate, or of Silver Proteinate (1 per cent.) and are used in amounts of 2 pints to treat dysenteric hæmorrhage and colitis. A simple antiseptic enema is a solution (4 per cent.) of Boric Acid, or 0·05 per cent. Potassium Permanganate.

Suppositories.—Suppositories provide another method of rectal medication. The Suppositoria Phenolis and Iodoformi are antiseptic and mild local anæsthetics. Suppositoria Acidi Tannici, Hamamelidis and Bismuthi Subgallatis are astringent. Belladonna Suppository relieves rectal spasm and the Morphine Suppository, which locally decreases rectal movements, will, after absorption, relieve pain; but, to relieve the pain and discomfort of internal hæmorrhoids, it is better to use Suppositoria Cocainæ. A Glycerin Suppository is useful as a lubricant and rectal stimulant and it facilitates the evacuation of hardened fæces.

Anal Ointments.—Unguentum Benzocainæ Co. (B.P.C.), by its local anæsthetic action, relieves the pain of anal fissure. Dilute Mercuric Nitrate Ointment is employed to discourage the migration at night of female threadworms from the large bowel in order to deposit their eggs on the peri-anal skin.

THERAPEUTICS

The most common symptoms of intestinal disorder are diarrhœa and constipation.

Diarrhœa may arise from excessive activity of either the small or the large intestine. In the former case, the stools are green because insufficient time elapses for the oxidation of biliverdin to stercobilin; in the latter case, the stools are normal in colour but contain much mucus. Diarrhœa may be due to (1) increased excitability of the peristaltic reflexes, as in nervous or lienteric diarrhœa; (2) increased irritability resulting from inflammation of the mucous membrane, which may be caused by irritants or micro-organisms in the food or by irritant products excreted into the bowel during disease, e.g. uræmia; and (3) alterations in the abdominal circulation, as in the chronic congestion of the mucous membrane associated with cardiac failure or hepatic cirrhosis.

Diarrhœa may be acute or chronic in character, the acute types being commonly associated with enteritis, the chronic with colitis. Acute diarrhœa often results from the ingestion of irritant substances or micro-organisms contained in the food. The degree of inflammation differs according to the type of irritant or micro-organism concerned, and may vary from a simple mucous catarrh to a severe and extensive ulcerative entero-colitis, such as occurs in the chronic diarrhœas caused by typhoid fever, dysentery and tuberculous or malignant disease.

In every case of diarrhœa the cause must, if possible, be removed. When the diarrhœa is severe, the patient, who usually feels cold, should be kept warm in bed, and loss of heat must be prevented especially when the bowels are moved. **Acute diarrhœa** due to irritants or organisms in the intestine is properly treated in its earliest stages by giving Castor Oil (1 fl. oz.) which rapidly clears the small and large intestines of harmful material, while the intestinal quiescence which follows is a valuable sequel. If indigestible food be the origin, its irritant residues can be removed by Rhubarb, the astringent action of which comes into effect after purgation has ceased.

Diet is of equal importance with medicinal treatment in diarrhœa. In acute cases, especially if vomiting occurs, food should temporarily be withheld in order to secure rest to the whole alimentary tract. Ice will serve to relieve thirst or sips of toast- or barley-water may be given, but liquids in large draughts must not be taken. When feeding is recommenced, tepid fluids consisting of broths or milk should first be given and, in order to obviate large indigestible curds, the milk should be given with Sodium Citrate or with Soda or Lime Water; to it starch, in the form of arrowroot or ground rice, may be added later. During recovery, particularly if the diarrhœa shows a tendency to become chronic, the diet must still be carefully selected, because recurrences are often due to dietetic indiscretions. The food should be carefully cooked and chosen so as to contain a minimum of fat, vegetables and seasoning; it should be taken slowly and at regular intervals. Foul-smelling alkaline stools suggest the presence of excessive putrefactive changes in the proteins, therefore these should be reduced and a more liberal allowance of carbohydrate arranged. Conversely, if the stools are frothy, acid and of sour odour, excessive fermentation of carbohydrates is taking place and these should be reduced in favour of more protein. The numbers of putrefactive organisms may be reduced by giving orally, in milk, cultures of Bacillus acidophilus which, by fermenting lactose, produce an alkaline reaction in the intestine. In obstructive jaundice, deficiency of pancreatic secretion, cœliac disease and sprue, the stools contain an excess of fat, hence this constituent must be eliminated from the diet. Polysaccharides are badly tolerated in the two latter conditions and must be largely curtailed.

After the administration of the initial purgative to empty the bowel, the **medicinal treatment of diarrhœa** consists mainly in the administration of drugs which diminish intestinal movements; these are, however, necessary only if the diarrhœa does not cease spontaneously. Pulvis Cretæ Aromaticus, given before meals or every four hours, is commonly employed; Light Kaolin and Bismuth Carbonate act similarly. These may be protective to the mucous membrane and they also adsorb toxins. Vegetable *astringents* which liberate Tannic Acid slowly, such as Krameria, and Catechu, may also be prescribed, preferably in the form of powders. Metallic astringents, such as the soluble salts of Iron and Lead, are less useful. With these protectives and astringents, a *neuro-muscular sedative* is usually prescribed, for example a small dose of a preparation of Opium, which diminishes peristalsis, contracts the sphincters and thus causes intestinal quiescence, and by its central action relieves pain. Preparations of this type are Pulvis Cretæ Aromaticus cum Opio, or Bismuth Carbonate or Light Kaolin may be given in suspension with a fluid preparation, e.g. Tinctura Opii or Tinctura Chloroformi et Morphinæ Composita. A *carminative* preparation may also be added with advantage; when powders are prescribed, Pulvis Cinnamomi is particularly suitable, and for mixture the Aquæ of Anethum and Mentha Piperita, or Tinctura Cardamomi Composita are prescribed; if a combined sedative and carminative action is desired, Aqua Chloroformi is substituted. Brandy or Port is occasionally used as a sedative carminative.

Intestinal antiseptics.—These are not usually necessary for mild attacks of diarrhœa, but in persistent infective types, Phthalylsulphathiazole, Succinylsulphathiazole or Sulphaguanidine should be given. Although their chief value is in bacillary dysentery, they are effective in reducing the bacterial flora, and are given as prophylactics against infections before colonic operations.

In neurotic spastic colon, the muscular spasm and colicky pain can be relieved by Papaverine or Atropine, but the neurosis also requires treatment. Enemas, and other than mild purgatives, e.g. Liquid Paraffin, should be avoided. In chronic ulcerative colitis; sedative and adsorbent powders, such as Light Kaolin, Charcoal and Bismuth Carbonate, together with Atropine or Papaverine if colic is present, may give some relief. Phthalylsulphathiazole, Succinylsulphathiazole, and Sulphaguanidine produce satisfactory results in a small proportion of cases. The following local treatment is also recommended for chronic ulcerative colitis; high rectal washes, given with the patient in the knee-elbow position; the fluid, in amount of ½ to 1½ pints, is allowed to flow in through a tube from a funnel with a minimum head of pressure and should be retained for longer periods as improvement proceeds. In severe cases the fluid should consist first of Normal Saline alone; when the irritability of the bowel subsides, as is shown by the decreasing frequency of stools and increasing tolerance of the enemas, Potassium Permanganate solution (1 : 5,000) should be used and the strength slowly increased to 1 : 1,000. Tannic Acid (1 : 1,000), Proflavine (1 : 200,000), and Silver Nitrate, Zinc Sulphate or Copper Sulphate enemas (1 : 5,000) may be advantageous at a later stage, but they require to be used with care because by irritating the mucous membrane, they may make the condition worse. During convalescence from colitis, the diarrhœa may be replaced by constipation; this is treated by adjusting the diet and giving Liquid Paraffin: irritant purgatives should be avoided lest they cause recurrence of diarrhœa.

The treatment of diarrhœa due to specific micro-organisms requires special consideration. In **cholera**, life is endangered both by absorption of the toxins of the vibrio and by the extreme dehydration; hence intravenous injections of Hypertonic Ringer's Solution (120 gr. NaCl in 1 pint) and plasma drips have markedly diminished the mortality from this disease. Suspensions of Kaolin, given by mouth, adsorb the toxins in the intestine. Some successful results are reported from the use of the less absorbable Sulphonamides. Cholera Vaccine has a prophylactic value only.

Bacillary dysentery is treated by large and repeated dosage with Phthalylsulphathiazole, Succinylsulphathiazole or Sulphaguanidine; all are satisfactory for Shiga and Flexner infections but the first two are more effective in Sonne dysentery. Carriers should also be treated by these Sulphonamides until the stools have been negative for a month. Warm saline enemas afford comfort and counteract dehydration; to them may be added 5 to 10 G of

Succinylsulphathiazole. Morphine or Pethidine serve to relieve the griping pains. Serum Antidysentericum (Shiga) should be given in severe cases of this type.

Amœbic Dysentery is commonly brought under control by four daily intramuscular injections of 1 gr. of Emetine Hydrochloride. Complete elimination of the parasite and its cysts from the colon is more difficult and is accomplished by giving in the first instance a ten-day course of Emetine Bismuth Iodide in 3 gr. enteric-coated capsules each night. This overlaps, or is followed by, a course of ten daily retention enemas of Chiniofon, using 10 fl. oz. of a 2 per cent. solution. Following the course of Emetine Bismuth Iodide a fifteen-day course of Diodoquin 8 gr. is given or a ten-day course of Carbarsone 3 gr. or of Acetarsol 4 gr., each administered three times daily by mouth.

Infective Diarrhœa in children is a potentially grave condition which may be prevented by avoidance of weaning during hot weather, by ensuring a pure milk supply, by eliminating flies and by segregating infective cases. Half-strength Normal Saline Solution or Ringer-Lactate Solution (45 to 60 min. Lactic Acid per pint) only is allowed by mouth until the diarrhœa has ceased and thereafter diluted separated milk or lactic acid milk is given: with continued improvement a half-cream milk is ordered. Dehydration is treated by intravenous injection by drip technique of Normal Saline Solution diluted with four parts of sterile distilled water, alternating with injections of Injectio Sodii Lactatis Composita (Ringer-Lactate or Hartmann's solution). The latter increases the alkali reserve without risk of alkalosis by slow conversion of the Sodium Lactate into Bicarbonate. Drugs given by mouth are of little value except in ileo-colitis, due to one of the organisms of bacillary dysentery, where the relatively inabsorbable Sulphonamides are specific. Favourable results have, however, been observed following the administration orally of Streptomycin in certain cases.

Nervous diarrhœa, which occurs from emotional stress, usually responds to treatment with Phenobarbitone or Bromides, Tinctura Chloroformi et Morphinæ (B.P.C.), or Codeine Phosphate. **Lienteric diarrhœa,** due to hyperexcitability of the gastro-colic reflex and occurring immediately after the beginning of a meal, is relieved by prescribing Phenobarbitone or Atropine.

Constipation is a usual accompaniment of acute febrile disease and is particularly intractable in meningitis. Its most obstinate form is observed in congenital megacolon, whereas in slowly progressing intestinal obstruction, constipation alternates with attacks of diarrhœa. Painful anal conditions, such as fissures and inflamed piles, produce spasm of the sphincter and retention of fæces in the rectum. Constipation is frequently associated with dyspepsia, of which it may be the cause.

In most cases of constipation there is no structural disease of the intestine; the symptom is due to faulty habits, hence the term "habitual" is appropriate. Habitual constipation has two main causes—irregular defæcation and a faulty dietary. If the desire to defæcate, normally aroused by the gastro-colic reflex before or shortly after breakfast, is resisted, it will cease to be experienced: the rectum becomes dilated and the retained fæces, owing to absorption of water, become hardened and difficult to pass. When the rectum alone is at fault, the case is one of rectal constipation or dyschezia; in children particularly this type may be due to an uncomfortable or high closet seat or to the low temperature of the apartment.

In constipation, the diet usually lacks a sufficiency of foods rich in cellulose, and frequently termed "roughage," which resist digestion and thus constitute a bulky mass to excite the peristaltic reflex. A milk diet, or one consisting largely of proteins and starchy foods, leaves insufficient residue to stimulate peristalsis. From this cause, constipation of the colonic type begins and the slow accumulation of fæces dilates the colon and the transverse colon becomes elongated downwards so that kinks may occur. Another factor in the development of this type is insufficient exercise; consequently, the abdominal muscles lose their tone, the portal circulation is less efficient and the neuromuscular reflexes of the intestine are less responsive.

The diet in constipation should consist of foods yielding considerable amounts of "roughage," such as green vegetables, fruits, porridge, and wholemeal bread. Fats, such as Olive Oil in salad, cream and butter, assist by lubrication of the upper bowel.

Purgatives are, however, usually essential in most cases of constipation in order to ensure at first regular evacuations of the bowel. An effective initial purgative to clear both small and large intestines is Pilula Colocynthidis et Hyoscyami, administered at night and followed, if necessary, by a saline purgative in the morning. The bowel having been emptied, it may be possible in mild cases to ensure regular evacuation subsequently by giving Liquid Paraffin as a lubricant, but in most cases the regular use of a mild colonic stimulant will be necessary until regular habits are re-established. The best purgatives for repeated use are Cascara, Aloes, Senna or Phenolphthalein. These are prescribed at night either as a draught, e.g. Elixir Cascaræ Sagradæ, Syrupus Sennæ, or, for convenience, more commonly as pills or tablets containing Extractum Cascaræ Sagradæ Siccum. Small doses of Nux Vomica, or Strychnine Hydrochloride, which augment the reflex excitability of Auerbach's plexus, may be added with advantage. To prevent colic, a volatile oil as a carminative, or small doses of Dry Extract of Belladonna or Hyoscyamus, can be used. The dosage should be reduced gradually and the purgative finally withheld as regular motions become established.

The more severe forms of rectal constipation are best treated by enemas of soap and water, commencing with 1½ pints and gradually reducing the volume until the rectum empties itself spontaneously. Alternatively, enemata of Glycerin may be used, beginning with 1 fl. oz. of pure Glycerin and using on subsequent days the same volume of fluid with progressively less Glycerin and more water. Olive Oil (1 fl. oz.) injected into the rectum or a Glycerin suppository at night will soften hard fæcal masses and ease their removal by an enema of soap and water next morning.

In the treatment of constipation, walking or cycling is a valuable exercise; massage and movements designed to raise the tone of the abdominal muscles are also of benefit.

Flatulence often gives rise to discomfort, and the accumulation of gases within the stomach or intestine may embarrass the heart and induce attacks of anginal pain. Intestinal flatulence results from fermentation and therefore the character of the food is often responsible. Flatulence also occurs when there is both diminished absorption and peristalsis; this is most severe after abdominal operations, in peritonitis, typhoid and pneumonia: grave forms are termed "meteorism."

Mild attacks of flatulence are readily relieved by treating the associated dyspepsia and by the administration of a carminative. This may be an aqueous preparation such as Peppermint Water, Dill Water or Infusion of Cloves, or, if a more powerful effect is desired, an alcoholic preparation such as Spiritus Chloroformi or Tinctura Cardamomi Composita may be chosen. Charcoal and Kaolin are valuable, especially in intestinal flatulence, since they adsorb gases.

When **meteorism** occurs, whey or albumin water only is allowed by mouth. Hot fomentations or cloths wrung out from hot water and sprinkled with Turpentine (Turpentine stupes) are placed on the abdomen; a rectal tube is passed and, if flatus is not voided, an enema consisting of 2 fl. dr. of Oleum Terebinthinæ in a pint of soapy water is given. A hypodermic injection of 0·3 to 0·5 Mil (5 to 8 min.) of Posterior Pituitary Injection, 1·2 mg (1/50 gr.) of Physostigmine Salicylate, or 0·5 mg (1/120 gr.) of Carbachol should also be tried with the rectal tube in position. These drugs produce powerful contractions of the intestinal muscle and hence they must be used with great care in typhoid, and avoided if obstruction be suspected.

Other Uses of Purgatives.—The large intestine is an important excretory channel, therefore hydragogue and saline purgatives are given to expedite the removal of toxic substances from the tissues. In uræmia, toxic nitrogenous derivatives are excreted by the bowel, hence Magnesium Sulphate, or other saline, is administered daily to maintain loose motions. In gout, chronic rheumatism and chronic nephritis, a daily saline or saline mineral water is frequently beneficial. It is usual to give a hypertonic saline purgative orally or by enema to relieve the headache of increased intracranial tension.

CHAPTER V

THE LIVER

PHARMACOLOGY

THE liver receives the products of digestion and performs important functions: (1) The amino-acids are in small amounts passed on to the tissues to replace protein katabolism in them; but the bulk is de-aminated by the hepatic cells to form urea and non-nitrogenous residues which are converted into sugars to provide energy for the tissues. (2) Glucose is converted by enzymes, assisted probably by Insulin, into glycogen, which is stored, and thus an excess of sugar in the blood is prevented; as it is required, the glycogen is hydrated by phosphatase to glucose. (3) The liver acts as the desaturating organ for the fats, which are first taken up from the blood by adipose and other tissues. (4) The bile salts, sodium taurocholate and glycocholate, which are formed by the liver cells, enhance the digestive action of the pancreatic enzymes, and, by a hydrotropic action, promote the absorption of fatty acids. (5) The bile pigments are excretory products which originate from the destruction of hæmoglobin by macrophages in the bone-marrow, spleen and liver. (6) The liver synthesizes fibrinogen and prothrombin which are essential for the clotting of blood, and, in its mast cells, the anticoagulant heparin; it stores reserve iron for the formation of hæmoglobin; and forms, from the product of the interaction between the "intrinsic factor" in the gastric juice and the "extrinsic factor" in protein, the anti-anæmic principle which in the bone-marrow is essential for the development of megaloblasts into normoblasts and reticulocytes. (7) The liver acts as a partial filter for alkaloids, toxins and metallic salts, which may be absorbed from the intestine; and the bile acts to a small extent in an excretory capacity, in that Iodophenolphthalein, Phenolphthalein, Hexamine and heavy metals are eliminated through it.

We can partly restrict the hepatic functions, particularly the production of urea and glycogen, by modifying the food supply, but as the chemical changes produced by the liver cells upon the products of digestion are intimately related to the metabolism of the body, this subject will be dealt with under General Metabolism.

The pharmacological control of the functions of the liver may thus be classified:

(1) **Drugs modifying the glycogenolytic function.**—(*a*) Glycolysis is *increased* by Adrenaline, Ephedrine and Thyroxine, Ether and Chloroform, which mobilize the hepatic glycogen. Phloridzin can cause an intense glycosuria, but this is due to prevention of reabsorption of excreted sugar by the renal tubules. (*b*) Glycolysis is *decreased* by Insulin, and in a minor degree by Morphine and Codeine when given by mouth.

(2) **Drugs modifying urea formation.**—(*a*) The excretion of urea is *augmented* by drugs which are readily converted into this compound, e.g. Ammonium Bicarbonate and the Acetates or Citrates of Ammonium. Ammonium Chloride is also excreted as urea while the chloride ion lowers the alkali reserve of the plasma. (*b*) The excretion of urea is *reduced* by acids or acid salts because the renal tubules, in order to protect the alkali reserve of the plasma, convert them into ammonium salts, which are excreted in the urine.

(3) **Drugs increasing biliary secretion.**—The only effective *cholagogues* are bile salts, and Sodium Taurocholate is a more active stimulant than the Glycocholate. Sodium Tauroglycocholate (B.P.C.), in doses of 0·12 to 0·4 G (2 to 6 gr.), increases biliary secretion, and aids absorption of Vitamin K. Extractum Fellis Bovini is recommended also as a cholagogue; both it and the Sodium Tauroglycocholate should be given either before meals or in enteric-coated capsules, so that they are not destroyed by the gastric juice.

(4) **The expulsion of bile** from the gall bladder can be examined by X-rays after the administration of Iodophenolphthalein by mouth or intravenously, or Pheniodol given orally in tablets. The emptying of the gall bladder is *accelerated* by the administration of fats, including egg yolk and Olive and Castor Oils, by mouth; some decomposition product of fats, when absorbed, appears to produce contraction of the gall bladder. Magnesium Sulphate, in hypertonic solution (33 per cent.), also causes the expulsion of bile into the duodenum, and irritant purgatives may reflexly relax the sphincter of the common bile duct and cause an increased flow of bile. These drugs are properly regarded as "indirect cholagogues." Purgatives, e.g. Calomel, which merely prevent

intestinal decomposition of the bile pigments so that the fæces appear to be stained with bile, are obviously not cholagogues.

THERAPEUTICS

Slight forms of impaired hepatic function are difficult to diagnose with certainty although probably common in the middle period of life. Sedentary habits, over-indulgence in rich food or alcohol, and constipation often combine to impair the important intermediate metabolic functions of the liver. In such cases, hygienic and dietetic treatment is most important. Regular exercise must be taken; the diet must be moderate in amount and easily digested; highly seasoned foods, game, cheese, curries and condiments should be avoided, and as a rule alcohol is forbidden. Dietetic indiscretions or drug toxicities may cause either an acute necrosis or a fatty infiltration preceding fibrosis or cirrhosis, especially if there is a dietetic defect of the sulphur-containing amino-acids cysteine and methionine which, as well as glucose, are important protectives against liver damage, including that from drugs.

Catarrhal jaundice or acute infective hepatitis is due to the invasion of the liver by a virus and closely resembles homologous serum jaundice; nausea, vomiting and constipation, which are prominent early symptoms, are accompanied by bilirubinæmia and followed by jaundice with biliuria and clay-coloured stools. Treatment consists in rest and warmth to reduce metabolism and in a diet containing adequate carbohydrate and protein but very little fat; skim milk, as its casein is a source of methionine, is very suitable in early stages. Saline purgatives are given to maintain clearance of the intestines. In jaundiced patients, prothrombin is deficient and Menaphthone or Acetomenaphthone should be administered for a few days before any operation is undertaken, or in any event if jaundice is prolonged.

Chronic Interstitial Hepatitis or Hepatic Cirrhosis is commonly of alcoholic origin. In early stages, abstinence from alcohol, rest in bed, gastric lavage with Sodium Bicarbonate if the secretion of mucus is excessive, saline purgatives and a diet with ample carbohydrate, easily digested protein and a minimum of fat, will lead to improvement or recovery. In late stages, ascites and œdema of the legs have to be treated by Injection of Mersalyl as a diuretic and by tapping. Methionine, Cysteine and Casein Hydrolysate have also been used with benefit.

Acute Yellow Atrophy or Liver Necrosis may result from infective hepatitis but it is also a risk from the use of the following drugs: Chloroform (delayed poisoning), Carbon Tetrachloride, Cinchophen, Arsenic, Neoarsphenamine and other Organic Arsenicals, Phosphorus, Antimony, Mercury, Gold and, in industry, trinitrotoluene and tetrachlorethane. Prevention is most important and the liver is protected by having an adequate reserve of glycogen as well as of the sulphur-containing amino-acids, Cysteine and Methionine. Treatment consists in giving Glucose injections intravenously, Methionine or Casein Hydrolysate intravenously or orally, and, for the metallic poisonings, Dimercaprol. Barbiturates or Morphine may be required to control the delirium.

Gall stones, in the majority of cases, require to be removed by surgical operation, since no remedy is known which will dissolve the calculi in the gall bladder. As the predisposing causes are biliary stasis, infection of the biliary passages, and perhaps hypercholesterinæmia, considerable relief may be given to cases, when the diagnosis is uncertain or operation contra-indicated, by treatment directed against these causes. Small meals should be taken frequently in order to produce frequent emptying of the gall bladder. Foods rich in lipoids, such as eggs, fats, liver, kidney, brain and peas, must be avoided and regular exercise encouraged; abdominal massage is of value in many cases. Drainage of the gall bladder is also promoted by giving 60 to 100 gr. of Magnesium Sulphate in concentrated solution before breakfast or Olive Oil half an hour before each meal.

Biliary colic is treated by the hypodermic injection of full doses of Atropine Sulphate, Papaverine, or Pethidine, which relax the muscular spasm; the latter two also mitigate pain, but Morphine with Atropine is more effective.

The appropriate remedy for amœbic abscess of the liver in dysentery is Emetine Hydrochloride intramuscularly or subcutaneously—1 gr. daily for 12 days—and, if practicable, the aspiration of the abscess and the injection into the cavity of a 0·2 per cent. solution of Emetine Hydrochloride in water.

CHAPTER VI

THE BLOOD

PHARMACOLOGY

THE blood performs important functions: (1) The supply of oxygen to the tissues is maintained from that in free solution (0·3 c.c. per cent. at a tension of 100 mm. Hg) in the plasma; this is replenished by dissociation of O_2 from hæmoglobin (which contains 18·2 c.c. per cent.) in response to the lowered O_2, and increased CO_2 tension in the tissues. (2) Sodium bicarbonate and proteins in the plasma form loose combinations with the CO_2 formed in the tissues and, by acting as "buffer salts," resist any increase in the H-ion concentration of the blood. (3) The plasma conveys nutrient materials, hormones and drugs to the tissues and excretory products to the kidneys. (4) The plasma contains and can develop immune bodies, e.g. agglutinins, bacteriolysins, opsonins, antitoxins, etc., which protect the organism against bacterial invasion.

The red corpuscles, besides conveying oxygen in combination with hæmoglobin to the tissues, also carry carbon dioxide which —when liberation of oxygen in the tissues lowers the acidity of hæmoglobin—combines with the potassium base of the feebly acid hæmoglobin and the phosphates in the corpuscles. Conversely, in the lungs oxygen, by forming the more acid hæmoglobin, displaces the carbon dioxide from combination with the base.

The red corpuscles are formed in the bone-marrow from megaloblasts which, under the influence of the anti-anæmic (hæmatopoietic) factor, Vitamin B_{12}, formed by the liver, mature into erythroblasts, and these require for their further development into normoblasts, reticulocytes, and erythrocytes, adequate amounts of Iron; probably also traces of Copper, Cobalt, Vitamin C, and Thyroxine play some part as stimulants. The red cells are ultimately broken up by the reticulo-endothelial tissues in the bone-marrow, spleen and liver to form the pigments of the bile and urine. The granulocytes or polymorphonuclear leucocytes, acting as phagocytes, assist in the protection of the body against bacteria.

Coagulation of the blood is dependent upon the conversion, by thrombokinase and calcium salts, of the prothrombin, formed in the liver, into thrombin which converts fibrinogen into fibrin. Vitamin K (Menaphthone and Acetomenaphthone) increases prothrombin formation.

The influence of drugs and other therapeutic measures upon the blood may be considered under the following headings:

1. The *volume of the blood* may be *increased* by rectal, hypodermic or intravenous injections of Injectio Sodii Chloridi (Normal Saline Solution), Injectio Sodii Chloridi Co. (Ringer's Solution), or, if a nutrient is required, Injectio Dextrosi (5 per cent.). These are valuable restoratives in dehydration, shock and hæmorrhage. If the alkali reserve must be increased, as in diabetic coma or infantile ketosis, Injectio Sodii Bicarbonatis (5 per cent.) or Injectio Sodii Lactatis Co. will be used. These act only temporarily because, the colloidal osmotic pressure of the blood being lowered, water is rapidly excreted by the kidneys.

Blood or plasma transfusion from a suitable donor is, however, the most effective way of restoring blood-volume but, as the plasma of some people causes agglutination of the corpuscles of others, it is essential first to "group" the blood of the recipient. Bloods of Group AB are universal recipients, while bloods of Group O may with relative safety be regarded as universal donors. For blood transfusion, 420 c.c. of the donor's blood is allowed to run into 120 c.c. of Injectio Sodii Citratis Anticoagulans or Injectio Sodii Citratis cum Dextroso or similar solutions containing Sodii Citras Acidus (*see* p. 44). Compatible whole blood, plasma and dried plasma for transfusion are available from blood banks. Reactions, e.g. shivering and fever, half an hour or later after injection of citrated blood are not uncommon but are rarely severe.

2. *Blood Gases.*—Since the oxygen dissolved in the plasma increases in proportion to the tension in the alveolar air, the amount in solution in the blood can be increased from 0·3 per cent. to 3 per cent. by means of Oxygen inhalations. Similarly, inhalation of Carbon Dioxide increases the tension in the arterial blood of this gas which stimulates the respiratory centre; a mixture of 5 per cent. Carbon Dioxide with 95 per cent. of Oxygen is used for this purpose.

3. *Neutral Salts of the Plasma.*—The normal salts of the plasma

may be *increased* for a brief period by giving soluble salts of Sodium, Potassium, and Calcium, but abnormal amounts are rapidly excreted. In treating Addison's disease, modification of the intake of Sodium and Potassium Chlorides is usually necessary (*see* p. 40). The *calcium content of the blood* may be increased by giving Calcium Lactate, Chloride or Gluconate, the latter two, if necessary, by injection; and the absorption and utilization of Calcium and Phosphorus by the tissues is promoted by the administration of Vitamin D in the form of Cod-Liver Oil or Calciferol. Administration of Parathyroid Extract, by mobilizing the calcium of the bones, also augments the calcium in the blood and over-secretion of Parathyroid increases the excretion of calcium and leads to softening of the bones (osteitis fibrosa).

4. The *alkali reserve or "buffer salts"* of the plasma may be *increased* by giving alkalis, such as the basic salts of Potassium, Sodium, Calcium or Magnesium, or in a moderate degree by alkaline mineral waters. Citrates and Tartrates also increase the alkali reserve because they are oxidized into carbonates. The effect is transient, however, because excess of bicarbonate in the blood is excreted in the urine; nevertheless, excessive use of alkalis will lead to alkalosis.

The alkali reserve can be *reduced* only with difficulty because the ammonia-urea metabolism intervenes. Administration of acids or acid salts will lower it for a time, but they are soon neutralized by the "buffer salts" or by ammonia formed by the renal tubules and excreted as neutral or acid salts. Ammonium Chloride or Nitrate also lowers the reserve, as the ammonium ion forms urea while the chloride or nitrate ion unites with some of the basic ions of the plasma; acid salts are excreted in the urine to restore the normal *p*H of the blood: Calcium Chloride and Ammonium Mandelate produce the same result. Reduction of the alkali reserve gives rise to acidosis.

5. *Coagulability of Blood.*—Coagulation time is believed to be accelerated by giving Calcium Gluconate or Lactate by mouth, and by intravenous injections of Hydrated Calcium Chloride in 1 per cent. solution or of Injectio Calcii Gluconatis (10 per cent.) Vitamin K (Menaphthone and Acetomenaphthone) increases the prothrombin content, if it is deficient, and restores normal coagulation time within two days; it is used in obstructive jaundice, sprue and infantile hæmorrhages. Transfusion of blood is often valuable in persistent and gastric hæmorrhage and in purpura hæmorrhagica. Various hæmostatic sera have been tried to

accelerate coagulation (*see* p. 455). Human Thrombin, Fibrinogen and Fibrin Foam or Film (*see* p. 456) are now used in surgery; Human Fibrinogen (2 per cent.), injected intravenously, reduces the coagulation time in hæmophilia and Russell's Viper Venom has been proved effective as a local application in hæmophilic bleeding.

6. The *internal secretions* of the thyroid, suprarenal, pituitary, pancreas, ovary, etc., can be given if they are deficient in the body, and the antibodies of the plasma can be augmented by means of vaccines and sera.

7. *Drugs which in anæmias increase the red corpuscles and hæmoglobin*, i.e. *hæmatinics.*—Hygienic principles, such as abundant assimilable food and exercise in fresh air and sunlight, are important in the prophylaxis and treatment of anæmias. The liver, as we have seen, carries a reserve store of Iron which is drawn upon in the regeneration of hæmoglobin after hæmorrhage, etc.

In *chlorotic and microcytic* (*secondary*) *anæmias* with reduced colour index, the administration of Iron by mouth is the curative treatment and it is now recognized that the inorganic preparations, and particularly the ferrous compounds, are more satisfactorily absorbed than the organic; but, because the absorption of Iron is slow and occurs only in the duodenum and upper jejunum, treatment must be continued over weeks or perhaps months, and the dosage of Iron should be more than ten times the daily needs (about 10 mg) of the body; and large doses, representing 0·4 G (6 gr.) of Iron, produce very successful results. The **relative astringency** of the preparations of Iron is important. The Scale Preparation—Ferri et Ammonii Citras—which does not precipitate proteins, is not astringent and, therefore, causes neither indigestion nor constipation. Pilula Ferri Carbonatis, Ferri Carbonas Saccharatus, being converted partly to chlorides in the stomach, have a mild astringent action, whereas Ferri Sulphas and Liquor Ferri Perchloridi are strong astringents. When Iron causes constipation, a regular aperient, such as the Elixir or Liquid Extract of Cascara, should also be prescribed. Syrupus Ferri Phosphatis Compositus may be used for children. Ferrivenin, a 2 per cent. stable solution of Saccharated Iron Oxide containing 100 mg Fe in 5 Mils is used by intravenous injection in severe cases with advantage; 100 mg raises the hæmoglobin deficiency by 4 per cent. (Haldane) hence the required total dose may be calculated but 50 per cent. extra should be given. Repeated injections are advised, as large single injections cause toxic effects.

Small doses (1/120 to 1/60 gr.) of Copper Sulphate may have an adjuvant action upon the hæmatinic effects of Iron in microcytic anæmias.

In *pernicious anæmia* and in the macrocytic anæmias of pregnancy and sprue, there is lacking the anti-anæmic factor; formed by the liver from a product of the digestion of proteins by the gastric juice; this factor stimulates in the bone-marrow the conversion of megaloblasts into erythroblasts. Vitamin B_{12} is the active principle (*see* p. 215). The anti-anæmic factor may be given by mouth in the form of Extractum Hepatis Liquidum in amounts equivalent to about 1/2 lb. of fresh liver daily or as Proteolyzed Liver (*see* p. 212); Desiccated Hog's Stomach is also effective in treatment. Folic Acid given orally, or its Sodium salt intramuscularly, is not so effective as Liver Extract and does not prevent subacute combined degeneration of the cord. The cheapest and most satisfactory treatment is intramuscular injections, e.g. Hepatex, Anahæmin, Campolon, of liver preparations from which the proteins have been removed. These are given daily for a few days, thereafter weekly, or in large doses monthly, with success. In severe cases initial blood transfusion may be required. The anti-anæmic factor causes a rapid increase in the reticulocytes in the blood and soon the numbers of erythrocytes and the amount of hæmoglobin increase—the latter more slowly—until a normal blood-picture and colour index is restored; the achlorhydria remains unaffected and requires separate treatment.

A *diminution of the red cells* and of hæmoglobin occurs in chronic poisoning from Mercury and Lead; Phenylhydrazine Hydrochloride and radio-active Phosphorus cause destruction of erythrocytes (*see* pp. 217, 95).

8. *Drugs which influence leucocytes.*—The numbers of leucocytes in the blood increase during digestion, and usually also following the administration of Bitters, Volatile Oils, etc., which promote intestinal absorption. Penicillin Injections are often valuable in agranulocytosis, Sodium Pentose Nucleotide in 8 per cent., solution (*Dose*—Intramuscularly 10 Mils daily) stimulates within five days the bone-marrow to increase granulocyte formation, and has been used in agranulocytosis; but severe reactions are common (*see* p. 217). Colchicum first diminishes and then greatly increases the granulocytes. Benzene and X-rays, which are toxic to lymphoid tissues, reduce the number of leucocytes, but the

effect is not permanent. Urethane, given orally, and Radio-active Phosphorus, or Nitrogen Mustards, given intravenously, are palliatives in chronic myeloid leukæmia and Hodgkin's disease.

9. *Drugs which alter Hæmoglobin.*—These are of interest only as poisons. Inhalation of carbon monoxide (coal gas) leads to the formation of carboxyhæmoglobin; Nitrites, Acetanilide, Phenacetin, or Potassium Chlorate in excessive doses and Sulphonamides may form methæmoglobin; while, in Sulphonal poisoning, hæmatoporphyrin is formed and is excreted in the urine. During Sulphonamide treatment, traces of sulphæmoglobin may be formed. These drugs may therefore interfere with the respiratory functions of the blood. Nitrous Oxide merely displaces oxygen in the blood temporarily and is readily eliminated from it.

10. *Drugs which are toxic to bacteria or kill Parasites in or through the Blood.*—The Sulphonamides and Penicillin are bacteriostatics against the species of organisms which are sensitive to them. The Sulphones give promise of improving lepromatous leprosy. Streptomycin is decidedly toxic to My. Tuberculosis while Chloromycetin and Aureomycin are effective against Rickettsias and certain viruses. The Organic Arsenicals, Neoarsphenamine, Sulpharsphenamine, etc., become, by undergoing slow oxidation in the tissues, toxic to the Treponema pallidum of syphilis. Bismuth salts, if injected, and Mercury salts are also toxic to this parasite. The Organic Arsenicals are toxic to the organisms of relapsing fever, rat-bite fever, frambœsia (yaws) and bronchial spirochætosis, and also to the guinea-worm. Antimony salts, Tryparsamide, Antrypol, and Aromatic Diamidines are toxic to the trypanosomes of sleeping sickness, while Antimony salts are also effective in leishmania infections, e.g. kala-azar, as well as in bilharziasis and filariasis. Quinine, Mepacrine, Pamaquin and Proguanil are specific for the malarial parasite.

11. *Vaccines and Sera.*—These agents are used to increase the resistance of the body to organismal diseases, and are employed both as prophylactics, e.g. smallpox or typhoid vaccines and diphtheria or tetanus toxins, etc., or as curative agents, e.g. diphtheria and tetanus antitoxins. Their actions are discussed on p. 447.

THERAPEUTICS

In this section, the treatment for disorders of the blood-cells and of coagulability only will be discussed; disorders of the chemistry of the blood are discussed under the therapeutics of metabolic diseases.

Anæmias fall into two main categories. In microcytic anæmias, there is inability to synthesize hæmoglobin owing to defective absorption or assimilation of Iron. In macrocytic anæmias, the bone-marrow is unable to form an adequate stroma for the red cells because an essential hæmopoietic principle (formed by the union of an extrinsic factor present in food proteins with a substance, the intrinsic factor or Castle's enzyme, secreted by the normal stomach wall), is absent. The principle is Vitamin B_{12}.

Microcytic anæmias result from many causes, the most important of which are malnutrition, hæmorrhage, infections, whether of bacterial, protozoal, or helminthic origin, and carcinoma. The treatment required in microcytic anæmias is a diet containing a generous allowance of red meat, green vegetables and fruit, which favour blood regeneration; constipation when present must be corrected by mild purgatives, e.g. Cascara or Aloes; and Acidum Hydrochloridum Dilutum is given if, as is not unusual, the gastric acidity be below normal. The administration of Iron is curative in microcytic anæmia but it must be given in adequate dosage and over a long period. The non-astringent scale preparations, Ferri et Ammonii Citras, should be given at first and followed by those which have little astringency, namely Pilula Ferri Carbonatis, Ferri Carbonas Saccharatus, or Syrupus Ferri Phosphatis Compositus. Pilula Ferri Carbonatis (Blaud's Pill), Tabellæ Ferri Sulphatis, B.P.C., and Tabellæ Ferri Sulphatis Co., B.P.C. (containing 1/25 gr. each of Copper and Manganese Sulphates) are particularly suitable preparations for ambulant patients and should be given in large doses each day. Small doses 1·2 mg (1/50 gr.) of Copper Sulphate and Manganese Sulphate are believed by catalytic action to promote Iron utilization.

Macrocytic Anæmias, such as Addisonian pernicious anæmia, the macrocytic anæmia of pregnancy and of tropical sprue, are treated by the intramuscular injection of Liver Extracts and the improvement maintained either by appropriately spaced injections of Liver Extracts or by the oral use of Extractum Hepatis Liquidum or Hog's Stomach. As the liver stores the hæmopoietic principle, intramuscular therapy is the most satisfactory and cheapest. Specially purified Liver Extracts, e.g. Neohepatex, Anahæmin, Campolon, Hepastab, etc., are available for intramuscular or intravenous injection in severe cases; they are usually given intramuscularly in the gluteal region in doses of 2

Mils, or the equivalent of 200 to 400 G liver, daily for four days and then at weekly intervals until full recovery of the erythrocytes and hæmoglobin is achieved. The restoration of a normal blood is important in Addisonian anæmia in obviating subacute combined degeneration. Thereafter, a maintenance intramuscular dose of the equivalent of 100 G liver or more is given at intervals of three to four weeks according to the needs of the patient. Patients, particularly during the recovery stages, should receive a preparation of Iron to aid hæmoglobin formation and possibly diluted Hydrochloric Acid with meals to replace its deficiency.

Folic Acid, although it has proved effective in the treatment of macrocytic anæmias, is not so reliable as Liver Extracts and it does not prevent the degenerative changes in the cord which are associated with Addisonian pernicious anæmia. Vitamin B_{12}, which is on trial, prevents subacute combined degeneration of the cord, in doses of 10–80 microgrammes (γ) intramuscularly.

For maintenance treatment, oral administration of Extractum Hepatis Liquidum, or Proteolyzed Liver, or a diet containing lightly-cooked liver may be adequate or assist by lengthening the intervals between intramuscular injections. Hog's Stomach preparations, which are thermolabile and should not be heated above 45° C., are also of service in maintaining improvements.

Aplastic anæmia, in which the activity of the bone-marrow is completely suspended, can be treated, if severe, only by repeated blood transfusion in the hope that the marrow may ultimately resume its hæmopoietic functions; Liver Extracts, Folic Acid and Iron may assist recovery. Benzene, Trinitrotoluene, Gold, Bismuth and Organic Arsenical injections, and radio-therapy may cause aplastic anæmia.

An excessive number of red cells in the circulation, as occurs in **Polycythæmia vera or erythræmia,** may be reduced by deep X-ray therapy, or by administering Phenylhydrazine Hydrochloride in doses of 0·1 G (1½ gr.) thrice daily. This drug rapidly destroys red blood-cells and should therefore be given cautiously in courses of seven days' duration followed by an interval of four days; the changes in the blood-picture must be carefully watched. Radio-active Phosphorus has produced some good results.

In **leukæmia,** the abnormal white cells in the blood and bone-marrow may be reduced in numbers by deep X-ray therapy and by Radio-active Dibasic Sodium Phosphate, given intravenously. Benzol, formerly used, is liable to cause aplastic anæmia. Urethane orally in doses of 2 to 5 G daily improves chronic myeloid leukæmia and to a less extent lymphatic leukæmia but rarely acute leukæmia. Nitrogen Mustards, given intravenously, act as palliatives also; chronic myeloid leukæmia and Hodgkin's disease seem to respond best. Liquor Arsenicalis also only ameliorates the condition for a time.

Malignant neutropœnia or agranulocytic angina is a condition in which, as a result of the toxic action on the bone-marrow of Amidopyrine, Dinitrophenol, Gold compounds, Tridione, Thiouracil, and rarely Sulphonamides and Phenacetin, the production of granular leucocytes is suspended. The associated sore throat is best treated by Penicillin Lozenges or Sprays and Penicillin by injection is usually curative in early cases. If this fails to produce improvements, Pentose Nucleotide, as Injectio Nucleotidi (B.P.C.) in 10 Mil doses is given intramuscularly twice daily for four to five days to stimulate granulocyte formation.

Hæmorrhage: hæmostatics.—Severe *external* hæmorrhage is arrested by surgical ligature. Hæmostatic or styptic measures may by classified thus: (1) Physical hæmostatics. These will include elevation of the part, etc., pressure by pads or tourniquet, application of cold water, or douching with hot water at 110° to 120° F., e.g. in post-partum hæmorrhage. (2) Protein precipitants, such as Tannic Acid or Lead Acetate, applied locally. (3) Peripheral vasoconstrictor stimulants, such as Adrenaline locally. (4) Direct stimulants of plain muscle, e.g. Pituitrin, or Ergot (Ergometrine) internally or intramuscularly in uterine hæmorrhage.

Drugs increasing the coagulability of the blood are desirable for the treatment of hæmophilia and purpura hæmorrhagica as well as when hæmorrhage is anticipated after operations or childbirth, or occurs in an inaccessible place. Calcium Chloride or Lactate or Calcium Gluconate are given orally, or Hydrated Calcium Chloride or Gluconate intramuscularly, both as prophylactics and as remedies for remote hæmorrhage, but with doubtful benefit. Hæmostatic Sera (*see* p. 455) are advised as intramuscular or intravenous injections, but they are rarely of advantage; blood transfusion is more often successful, particularly in purpura hæmorrhagica. Vitamin K, intramuscularly as Injectio Menaphthoni or orally as Tabellæ Acetomenaphthone, restores the prothrombin level in obstructive jaundice, sprue and neo-natal hæmorrhages. In hæmophilic bleeding, Russell's Viper Venom, "Stypven," or "Rusven" in 1:10,000 solution, applied locally, is a powerful accelerator of coagulation; if the bleeding-point is not accessible, 10 Mils of a 2 per cent. solution of Fibrinogen are injected intravenously. Fibrin Foam with Thrombin is used as a hæmostatic in surgery.

If the seat of hæmorrhage be *internal* and inaccessible—for example in the lungs—bodily and mental rest are secured by giving Morphine hypodermically. Hæmoptysis often ceases spontaneously but the induction of artificial pneumothorax or pneumoperitoneum may be considered if the bleeding persists or is profuse or recurrent.

Hæmorrhage from gastric ulcer is also frequently checked by allaying restlessness and securing bodily quietude by giving Morphine and by withholding food and drink by mouth for two or three days. Liquor Adrenalinæ Hydrochloridi (1 fl. dr. in 1 or 2 fl. oz. of Normal Saline) or Ephedrine Hydrochloride (1 gr. in 1 fl. oz. of water) by mouth is sometimes of advantage.

Post-partum hæmorrhage may be treated locally by hot-water douches and by the injection intramuscularly of Posterior Pituitary Extract, or Ergometrine.

Heparin, which delays coagulation time from 6 to 14 minutes, is used for the prevention and treatment of thrombosis, and is injected intravenously four times daily or is given by continuous intravenous infusion because its effect is brief. Dicoumarol, which reduces prothrombin formation, is given orally and begins to increase coagulation time after 24 hours; it is also used to prevent extension of clot in thromboses.

CHAPTER VII

METABOLISM

PHARMACOLOGY

THE arterial blood conveys oxygen, glucose and amino-acids to the active tissues, and the venous blood removes from them the superfluous metabolic products, e.g. carbon dioxide, lactic acid, creatinin and urea. Except during growth, the income in food is normally in equilibrium with the excretion of carbon, nitrogen and water; but carbon may be retained as fat; during exertion, owing to increased katabolism, greater excretion of carbon may occur.

Carbohydrates are absorbed as glucose and, with the aid of Insulin, stored as glycogen in the liver and muscles; the glycogen, when required for energy, is reconverted into glucose, which is oxidized in the tissues through pyruvic aldehyde and lactic acid into water and carbon dioxide. Insulin and the diabetogenic hormone of the anterior pituitary have important influences upon carbohydrate metabolism.

Fat is conveyed by the lacteals and blood to adipose tissues for storage but some is built up into lipoids. When required for energy or maintenance of heat, the fat is reconverted by oxidation into its components and in the liver the lower fatty acids, butyric, β-hydroxybutyric and diacetic acids are formed; these are oxidized in the tissues into acetic acid and finally into carbon dioxide and water. Carbohydrates are essential for the metabolism of fats and 1 G of Glucose can burn from 1 to 4 G of fat.

Small amounts of the amino-acids, derived from protein, act as metabolic stimulants and also reconstruct effete tissue proteins, which are broken down into creatinin, ammonia and urea (endogenous metabolism). Most of the amino-acids are deaminized by the liver and the nitrogenous portion is excreted as urea, while the non-nitrogenous portion is used by the tissues (exogenous metabolism). Purins, derived from nuclein, are converted into uric acid, which may be exogenous or endogenous in source, and, although it is convertible by a liver ferment into allantoin and carbon dioxide, it is normally excreted as urates.

The *Basal Metabolic Rate* or *Basal Metabolism* is the energy produced by a person at complete rest, and is measured indirectly from the percentage of carbon dioxide in the expired air. The basal metabolism may be influenced in various ways:

1. **Food.**—The utilization of the essential principles of diet has already been explained. During growth, pregnancy and lactation, and strenuous exercise as well as after exhausting illnesses, a liberal and well-balanced diet, consisting of meat, carbohydrates, fats and vegetables, must be provided so as to supply not only the requisite principles but also the vitamins which are essential in maintaining growth and health. Since proteins, owing to the amino-acids, glycine, alanine, etc., have a specific dynamic action in stimulating metabolism, they should be allowed freely during periods of strenuous exertion. Fats and alcohol, by lowering nitrogenous metabolism, act as sparers of protein.

2. **Tissue Oxidation.**—Deficiency of oxygen impairs the metabolic activity of the tissues; anoxæmia may arise in anæmias and other conditions which require appropriate treatment in order to overcome this defect.

3. **Exercise and Massage.**—Increased work augments the metabolic rate; hence manual workers require more food than those in sedentary occupations. Massage and passive movements also increase metabolism by increasing circulation in the tissues and improving their functional activity.

4. **Temperature, Climate, Baths.**—The influence of these external factors is essentially that of temperature. In a cold atmosphere, metabolism is increased so as to maintain the body temperature; conversely, external warmth lowers metabolism. Cold bathing and mountain or sea resorts, where there is a free current of air, are, therefore, regarded as bracing; while hot baths and warm, moist climates with stagnant air are found to be relaxing and enervating. Exposure to the ultra-violet rays of the sun, of mercury vapour or carbon arc-lamps stimulates metabolism, and diathermy accelerates metabolism so that the body temperature increases.

5. **Drugs.**—Many drugs, after absorption, modify the cellular metabolism; thus, probably by some physico-chemical surface action, anæsthetics and hypnotics abolish the normal activity of nerve cells which become completely restored in function when the drug is excreted or destroyed. Some drugs alter the metabolic

functions of particular cells only, e.g. Bromides select motor cells, Morphine sensory cells, Pilocarpine the cells controlled by parasympathetic nerves and Adrenaline those governed by sympathetic nerves. These actions may be due either to an extracellular influence, e.g. upon surface tension, or to intracellular changes in the protoplasm.

Drugs which influence metabolism.—The influence of many drugs upon the basal metabolism is negligible or secondary to their more important actions; thus the increased reflex excitability caused by Strychnine will raise the basal metabolism slightly while hypnotics, by inducing rest, will lower it. The **basal metabolism is increased** by Iodides, Thyroid, Adrenaline, Dinitrophenol and by large doses of Salicylates. Iodides and Thyroid are of importance for the treatment of cretinism and myxœdema where the basal metabolism is low owing to deficiency of the thyroid hormone. Adrenaline is used to stimulate the glycogenolytic function of the liver after overdosage with Insulin in diabetes; the action of Adrenaline results from its stimulation of the glycogenolytic (sympathetic) nerves. As, however, the glycogen of the liver is already depleted in hypoglycæmia, Pituitrin, which reduces the metabolism of glucose by the tissues, is also an antagonist of Insulin. Thyroid also raises the blood-sugar, probably by exciting an output of Adrenaline.

The **basal metabolism is lowered** by Alcohol, Chloroform, the organic hypnotics and by Morphine and Codeine. In thyrotoxicosis, Liquor Iodi Aquosus, Thiouracil and Methyl Thiouracil reduce the basal metabolic rate. Alcohol, by acting as a substitute for carbohydrates and fats, reduces the protein autolysis, hence it is sometimes given as a source of energy and as a sparer of protein katabolism in continued fevers. Morphine and Codeine also decrease protein katabolism and diminish the glycogenolytic function of the liver; this latter effect, which was formerly employed in the treatment of diabetes, is greater when they are given by mouth.

Insulin, the hormone of the β-cells in the Islets of Langerhans, controls carbohydrate and, through it, fat metabolism. It increases the utilization of glucose by the tissues, assists the storage of glucose in the form of glycogen by the liver and muscles, and checks the formation of sugar from proteins. It is probable that Adrenaline assists in mobilizing the hepatic glycogen so as to maintain the blood-sugar at a constant level.

Insulin has no action if given by mouth but, if injected, it reduces the percentage of blood-sugar. In a fasting man of 65 Kg (10 st.) weight, a dose of 5 to 10 Units will lower the blood-sugar from 100 mg per cent. to 50 mg per cent. The maximal reduction in the blood-sugar percentage occurs usually from two to three hours after the Insulin is given, and after about six to eight hours the blood-sugar returns to its previous level.

More prolonged effects are gained from Globin Insulin with Zinc, which begins to act in about three hours with a maximal effect from the fifth to eighth hours and a return to the former level in about eighteen hours; or from Protamine Zinc Insulin which acts in about four hours, has a maximal action during the eighth to fifteenth hours with recovery of the usual level after twenty-four to thirty hours. By using these preparations, the Insulin dosage can be spaced more widely and rapid variations in the blood-sugar curve avoided, but, as their action begins slowly, it may be necessary to give along with the insoluble forms some soluble Insulin to provide for the next meal. Di-insulin acts soon, like Insulin, but lasts for about eleven hours.

In diabetes, each Unit of Insulin should enable patients to take from 4 to 5 G additional carbohydrate. Owing to the increase in the carbohydrate metabolism produced by Insulin, fat metabolism is also augmented; therefore lipæmia and the lower fatty acids (butyric, β-hydroxybutyric and caproic) are removed from the blood, the condition of acidosis is counteracted, and ketone bodies—aceto-acetic-acid and acetone—disappear from the urine.

In man, if the blood-sugar level falls below 70 mg. per cent., symptoms of hypoglycæmia appear; these are anxiety, faintness, muscular tremors, sweating, rapid pulse, abdominal pains, followed by coma or, in children, fits; sometimes, adults become obstreperous, resembling alcoholics. After soluble Insulin, the onset is rapid; but with the insoluble forms it is slow and insidious. These symptoms can be cured by administering Glucose by mouth, rectally, or intravenously, or by 10 to 15 min. of Injectio Adrenalinæ which mobilizes the hepatic glycogen, or 5 min. of Injectio Pituitarii Posterioris which reduces the metabolism of glucose in the tissues. Hypoglycæmic symptoms may occur also in diabetics after Insulin from a sudden fall in their excessive blood-sugar level although this may still be above normal.

Drugs influencing Uric Acid Excretion, etc.—Uric Acid, which is formed from purins in the diet, is partly destroyed in the tissues and partly excreted as urates. Excessive formation of uric acid may lead to its deposition in the tissues as urates in gout, especially if the renal threshold for uric acid is increased, or to its excessive excretion in the urine as urates or uric acid, which may cause gravel or calculus. In these conditions the purins in the diet should be reduced, the intake of fluids increased, and diuretics prescribed, e.g. Potassium Citrate, which will decrease the acidity of the urine. Lithium salts, which were regarded as increasing the solubility of uric acid, have little pharmacological effect. Cinchophen, which lowers the renal threshold for uric acid, does reduce the uric acid content of the blood and increases its excretion by the urine, but may cause acute necrosis of the liver, if given for more than four days at a time.

Oxaluria, which may be exogenous, e.g. from vegetables such as rhubarb, or endogenous, e.g. from gastric fermentation of carbohydrates in achlorhydria, is remedied by dietetic treatment. *Phosphaturia* is commonly a result of diminished urinary acidity, and can be treated by amending the diet or giving Ammonium Chloride.

Vitamins.—Lack of Vitamin A in infancy retards growth, and, in adults, may cause night blindness and impair the protective epithelial tissues. Lack of Vitamin D leads to imperfect calcium and phosphorus assimilation and therefore to rickets and imperfectly calcified teeth. These Vitamins are available in Cod-Liver Oil, milk and butter. Beri-beri is due to insufficient Vitamin B_1 or Aneurine Hydrochloride, which can be obtained from yeast, cereals, etc., and pellagra to lack of Nicotinic Acid; while Vitamin C or Ascorbic Acid, the preventive of scurvy and important also for the formation of collagen, is present in rose-hip syrups, fresh fruit and vegetables. Vitamin K, Menaphthone or Acetomenaphthone, increases the prothrombin content of blood.

THERAPEUTICS

A brief description only of this large subject can be given.

Preventive Treatment.—In order to obviate or alleviate such conditions as alimentary glycosuria, obesity or uric acid diathesis, the diet should be so regulated that its amount is not excessive and that a proper relationship is maintained in the amounts of protein, carbohydrate and fat ingested. At the same time sufficient exercise must be taken to produce katabolism by the tissues of the products of digestion. When active exercise cannot be taken, it should be replaced by massage and passive movements.

Remedial Treatment.—When metabolic disorder exists, the cause must be sought and eliminated if possible. In **obesity** the amount of carbohydrate and fatty food is restricted and muscular exercise increased either by massage and passive movements in severe cases, by light gymnastics, or by walking, riding and outdoor games. Alcohol must be avoided. Thyroid, which powerfully increases the basal metabolism, has been used with success, but its action must be closely watched lest hyperthyroidism occur. Dinitrophenols are too dangerous for general use. The administration of saline purgatives is often of value in obesity; and alkaline waters, which decrease the pancreatic secretion, are the basis of spa treatment at Harrogate, Buxton, and Marienbad.

Alimentary glycosuria is successfully treated by diminishing the amount of carbohydrate food. **Renal glycosuria** is of small importance and rarely calls for treatment; Insulin is here contra-indicated as the blood is hypoglycæmic.

Diabetes mellitus demands careful clinical investigation and treatment by diet, and, *if necessary*, Insulin. The patient should at first be in bed, and it is well to estimate the fasting blood-sugar and the degree of glycosuria as guides. Dietetic treatment is of first importance, and several excellent schemes indicating the weights of different foods necessary to provide a correctly balanced diet are available. Enough protein (0·5 G per lb. body weight) to replace tissue loss must be included.

It is usual now to give a much higher ratio of carbohydrate to fat than was formerly allowed, because it has been found that the patients keep in better health and are less likely to depart from the prescribed diet, which can be more varied and less expensive. Thus to yield 2,000 calories, 150 G carbohydrate, 80 G protein, and 100 G fat is a commonly accepted ratio. As a Unit of Insulin can ensure the metabolism of 4 to 5 G of carbohydrate, this higher carbohydrate diet requires comparatively little more Insulin in order to keep patients sugar-free than was the case when it was the practice to prescribe a low carbohydrate and high fat diet.

A common procedure is to place the patient from the beginning on a maintenance diet and, if he be a mild case, his urine will remain free from sugar. In severe cases the urine will be found still to contain sugar and it will then be necessary to inject Insulin. Beginning with 5 Units before the principal meal, the dose of Insulin is increased by 2 to 5 Units every second day until the urine is free from sugar. Insulin is best given twice or thrice daily, the last dose at least four hours before bedtime, lest hypoglycæmia should occur during sleep. An alternative method of treatment—after a brief period of starvation during which the patient's urine usually becomes free of sugar—is to build up the diet gradually, Insulin being given at the stage when sugar first appears in the urine. Its dose is thereafter increased in proportion to the addition of carbohydrates until the level of a maintenance diet is reached.

Protamine Zinc Insulin, being absorbed more slowly than Insulin, can influence the blood-sugar level for as long as twenty-four to thirty hours, so that with the same Unit dosage and careful dietetic adjustment only one injection daily before breakfast is necessary, but it may require to contain a small proportion of soluble Insulin to control the carbohydrate taken during breakfast. Owing to the slower action of Protamine Zinc Insulin, the warning symptoms of hypoglycæmia may be unperceived and convulsions or coma may develop during the night. Globin Insulin, with Zinc, has an action intermediate between soluble Insulin and Protamine Zinc Insulin and, of it, only a morning injection in suitable cases may be necessary.

Ambulant patients should carry a supply of sugar or Medicinal Glucose to counteract attacks of hypoglycæmia. Broadly speaking, Insulin is indicated in the diabetes of children and persons under forty, in cases where intercurrent disease causes lowering of sugar tolerance, or where sugar tolerance is so low that the restricted diet is insufficient for existence, in diabetes before surgical operations, and in diabetic coma.

Diabetic coma requires treatment with Insulin in large doses (20 to 40 Units) as soon as possible; at the same time, the dehydration from which the patient always suffers must be treated by liberal administration of fluids orally or intravenously, and the bowels must be emptied by an enema. The blood-sugar is always high, but, if its level be unknown, 50 G of Glucose may be given with 40 Units of Insulin. If there is no recovery in two to three hours, 40 Units more of Insulin are given and a sample of urine is obtained; if this still contains sugar, more Insulin may be given, but, if sugar be absent, Insulin should be withheld till sugar reappears. Sodium Bicarbonate by mouth (120 gr. every four hours up to 1 oz.) hastens the removal of the acidosis, but if the patient is unconscious, Injection of Sodium Bicarbonate, or better Ringer-Lactate Solution, will be given intravenously. Surgical operations on diabetics should be performed only if the blood-sugar has been lowered to normal and after giving 25 Units of Insulin and 50 G Glucose two hours before operation. Any infectious disease, "cold," or influenza invariably lowers sugar tolerance and demands increased doses of Insulin.

In **uric acid diathesis and gout** the amount of protein and nuclein should be curtailed, alcohol interdicted and free action of the bowels and kidneys promoted. As remedial measures, alkalis and saline diuretics are administered to increase the alkali reserve of the blood, to lower the acidity and to augment the quantity of urine—an endeavour to promote the formation of urates and the solution of uric acid. The theory that, because potassium and lithium biurates are more soluble than sodium biurate, carbonates or citrates of these metals would be useful to dissolve deposits of biurate in gout, has been disproved. Cinchophen, which reduces the uric acid in the blood by increasing its excretion by the kidney, is valuable in many cases of gout, arthritis and muscular rheumatism, but it should not be given for more than four successive days without an interval, as it is apt to induce acute necrosis of the liver. Attacks of acute gout are relieved by Colchicine or Tincture of Colchicum, but by what action is unknown. Locally the joints must be protected from pressure by cotton-wool; hot fomentations and Cataplasma Kaolini also give some relief from the pain.

Deficiency Diseases may be cured in early stages by supplying the deficient Vitamin. For undersized children, or cases of xerophthalmia and night blindness, Vitamin A can be given in the form of Halibut Liver Oil, Liquor Vitamini A Concentratus, or by increasing the amounts of whole milk, butter and eggs in the diet. Similar modification of the diet is the essential treatment for rickets, defective calcification of the teeth and osteomalacia, but additional Vitamin D is advisable in the form of Cod-Liver Oil, Liquor Vitamini D Concentratus, or Calciferol; if possible, the patient should be transferred to a more sunny atmosphere or exposed to ultra-violet rays; treatment with Vitamin D is also of value in tetany. In beri-beri and toxic neuritis, Aneurine Hydrochloride, which is contained in yeast, wheat germ, or rice polishings, should be administered by subcutaneous or intramuscular injection at first and later, or for prophylaxis, as tablets; for pellagra, Nicotinic Acid or Nicotinamide in tablet form is given; and in infantile or adult scurvy, Ascorbic Acid or the fruits, lemon, orange, and tomato, or rose-hip syrup, which contain it, are required. Vitamin P (Hesperidin) has improved some types of purpura, and Vitamin K (Menaphthone or Acetomenaphthone) is valuable in the hæmorrhagic diathesis of obstructive jaundice and of infants.

Cretinism and **myxœdema** are rationally treated by arranging permanent treatment with Thyroid tablets. Simple hyperplastic **goitres** occur in districts where water is deficient in iodides; the administration of graded doses of Iodides leads to reduction of the enlargement. In **thyrotoxicosis** thyroid treatment is contra-indicated. Thiouracil, or better Methylthiouracil, after a delay of ten days, effectively controls the symptoms of thyrotoxicosis and sometimes produces a satisfactory remission so that dosage may be stopped; or a maintenance dosage may be established but patients should be under observation during treatment for possible toxic effects (leucopenia or agranulocytosis). Liquor Iodi Aquosus (Lugol's Solution), probably by saturating the incompletely iodized Thyroxine in this condition, reduces the hyperplasia of the gland and the basal metabolic rate, slows the heart rate and relieves the nervous symptoms. Lugol's Iodine is much used preparatory to the operation of subtotal thyroidectomy which is the treatment of choice in a proportion of the cases. Exposure of the thyroid gland to X-rays has been helpful in the past but is now rarely employed.

In **Addison's disease** the suprarenal glands are slowly destroyed, usually by tuberculous infiltration. The lack of the suprarenal cortical hormone which this occasions leads to excessive loss of sodium and a train of symptoms and signs which include low blood-pressure, pigmentation, hypoglycæmia, severe gastro-intestinal disturbance and dehydration. In mild cases considerable relief is afforded by a diet high in sodium and low in poitassium supplemented by Sodium Chloride in 10 to 15 G doses daily. Desoxycortone Acetate provides satisfactory replacement therapy in the severer cases. It is given in oily solution by injection, 10 to 25 mg daily in crisis and 2 to 5 mg daily for maintenance. For maintenance purposes Desoxycortone Acetate can also be implanted in the form of pellets in the subcutaneous tissue of the abdominal wall. An implant of 200 mg usually suffices to keep the sufferer from Addison's disease in normal health for about six months. When Desoxycortone Acetate is given, it is usually necessary to reduce the intake of Sodium Chloride.

CHAPTER VIII

THE CIRCULATORY SYSTEM

PHARMACOLOGY

1. PHYSIOLOGICAL CONTROL OF THE CIRCULATION.—The **cardiac muscle** contracts rhythmically when supplied with an oxygenated isotonic solution containing balanced proportions of salts. The official Ringer's Solution (Injectio Sodii Chloridi Co.) contains Sodium Chloride 0·86 per cent. which renders the fluid isotonic, while the Na ions maintain excitability; Hydrated Calcium Chloride 0·048 per cent., because Ca ions increase contractility and tone; and Potassium Chloride 0·03 per cent., as the K ion induces relaxation during diastole; to these ions, Sodium Bicarbonate 0·02 per cent. may be added to make the solution alkaline, and Glucose 0·1 per cent. as a source of energy. The salts in this solution excite the *sino-auricular node*, a neuro-muscular structure at the junction of the great veins and auricle, to rhythmic activity; the contraction wave passes through the auricles to the ventricles by the auriculo-ventricular bundle of His; travels first to the papillary muscles, then through the septum to the apex; and returns to the base in the region of the pulmonary artery by the spiral fibres. Between the auricle and ventricle is a second node of neuro-muscular tissue, the auriculo-ventricular node, which is capable of originating a rhythm of its own. The contraction of cardiac muscle gives rise to electrical currents which are examined in man by the electro-cardiograph. The positive wave of auricular activity (P) is succeeded by contraction of the auricle, and followed by an electrically quiescent period showing the time of transmission through the bundle of His (**P-R** interval); the second series of waves indicates the commencement of ventricular activity (QRS) and is followed by a second period of quiescence or equipotential, when the current is passing in all directions through the ventricle and neutralizes itself; the final variation (T) indicates the return of the contraction wave to the base by the spiral fibres.

The contractions of the heart may be modified: (*a*) by the frequency of the rhythmic stimuli, (*b*) by the rapidity of their conduction, (*c*) by the excitability of the muscle, (*d*) by the contractile force of the ventricle, which is directly proportional to the length of its muscle fibres at the end of the preceding diastole, and (*e*) by its tone.

The *movements of the heart are regulated* by the vagus centre in the medulla through the vagus nerves and by the sympathetic from the 2nd, 3rd and 4th dorsal nerves. Both nerves have cell stations, the vagus in the basal ganglia of the heart, the sympathetic in the ganglion stellatum. Stimulation of any portion of the vagus leads to prolongation of diastole and slowing of the rhythm or temporary inhibition, and to reduction of the tone, contractility and conductivity of the muscular fibres. Stimulation of the sympathetic has the opposite effects and results in acceleration and increased systolic force. Section of the vagi produces acceleration of the heart, showing that the vagus centre exerts a continuous control over the cardiac rhythm. A slow rhythm is usually due to an increased diastolic interval which signifies longer rest, and ensures better nourishment of the heart through the coronary arteries.

The *vagus centre* may be stimulated reflexly, and the heart slowed, by afferent impulses from irritation of the sensory nerves of the nose, larynx and lungs, peritoneum and viscera, or of the skin. Psychical impressions may increase or decrease the activity of the centre. The vagus centre is also influenced reflexly through the sinus and aortic nerves by sensory impulses derived from the *carotid and aortic bodies*. These bodies are chemo- and pressure-receptors which are influenced by changes in CO_2 and O_2 tension, in H-ion concentration, and in blood-pressure. Afferent impulses from them, caused by a rise in blood-pressure, slow and weaken the heart, and lower blood-pressure, the last effect being due partly to reflex vaso-dilatation through the vaso-motor centre. Excess of CO_2, defect of O_2, or increased H-ion concentration produces reflexly increased respiration, associated with acceleration of the heart and a rise in blood-pressure. Acetylcholine, Nicotine and Lobeline produce similar effects by an action on the carotid and aortic bodies.

Afferent fibres from the great veins are stimulated by a rise in venous pressure which reflexly depresses vagal tone and the heart accelerates.

The **arterial muscle** possesses a normal degree of tone which is controlled by the vaso-motor centre in the medulla through the *vaso-constrictor* and the *vaso-dilator* nerves and partly maintained by the sympathetic hormone, adrenaline, which is secreted at the vaso-constrictor endings in response to impulses from the vaso-motor centre. The *tone of the arteries* maintains the blood-pressure and provides for the steady flow of blood through the capillaries. When organs require more blood, their vessels are dilated and, to prevent alteration of the blood-pressure, vaso-constriction occurs in other parts, e.g. muscles.

The *vaso-motor centre* is stimulated reflexly by reduced CO_2 tension and lowered blood-pressure through impulses from the aortic and carotid bodies, and by sensory impulses and psychical factors, e.g. emotion. *Afferent impulses* from increased pressure in the heart and aorta depress the vaso-constrictor centre, and thus lead to a fall in blood- and intra-cardiac pressure.

The *general blood-pressure* is dependent: (1) on the cardiac output; (2) on the elastic recoil of the aorta; (3) on the arterial tone, which determines the peripheral resistance; and (4) on the volume of the blood in the body.

The **capillaries** effect the distribution of blood to the tissues. Their thin endothelial walls permit the passage into the tissues of plasma and leucocytes, and allow of metabolic exchanges taking place.

The **veins** are influenced physically—by posture, muscular movements, respiratory activity, and by the cardiac output and blood-pressure. They are innervated by the sympathetic and constrict to pressor reflexes and increase of CO_2 tension. During inspiration the increased negative pressure in the chest dilates the great veins and thus promotes the venous return flow.

2. PHARMACOLOGICAL CONTROL OF THE CIRCULATION.—Many methods and drugs are utilized in order to modify the physiological control of the heart and arterioles.

1. *The volume of the blood*, which is important for the maintenance of blood-pressure, may be *increased* by the intravenous, intramuscular or rectal administration of Normal Saline or Ringer's Solutions and by transfusion. The blood-volume can be *diminished* by venesection or by draining fluid from the body by hydragogue purgatives or diuretics.

2. *The heart.*—The heart may be influenced indirectly through its nerves—the vagus and sympathetic—or directly by an action on the muscular tissue.

(*a*) CARDIO-INHIBITORY MECHANISM.—(i) **The vagus centre** in

the medulla is stimulated directly by the glycosides of Digitalis, Strophanthus (Ouabain), and Squill; Strychnine and Caffeine may also produce slowing of the heart by central stimulation. *Indirect or reflex stimulation of the vagus centre* occurs from afferent impulses coming from the carotid and aortic bodies in response to increases in CO_2 tension, H-ion concentration and blood-pressure; it is in this indirect way that Adrenaline and Ephedrine may produce slowing of the heart. The vagus centre can also be stimulated indirectly by nervous reflexes originated by inhalation of irritant vapours, e.g. Chloroform or Ether, and by sensory stimuli applied to the skin, etc. The *vagus centre is depressed* and the heart accelerated indirectly, by reducing blood-pressure, e.g. through the action of the Nitrites.

(ii) **The vagus ganglia in the heart.**—The inhibitory ganglia are probably in close association with the sino-auricular node. They are stimulated by Nicotine, and Lobeline, which in small doses slow the heart whereas large doses of these and also Curarine depress the ganglia and cause acceleration of the heart.

(iii) **The vagus nerve endings in the cardiac muscle** are powerfully *stimulated* by Acetylcholine, Carbachol, Physostigmine, Neostigmine, Pilocarpine, Muscarine and Arecoline, and to a slight extent by Digitalis, Strophanthus (Ouabain) and Squill. The vagus nerve endings are *depressed and paralysed* by Atropine and its related alkaloids, Hyoscyamine, and Hyoscine.

Stimulation of the vagus causes slowing of the heart—mainly by prolonging diastole—and a decrease in contractile force, in muscular and A-V conductivity and in tone. Paralysis or section of the vagus produces the reverse effects.

(*b*) CARDIO-ACCELERATOR MECHANISM.—An accelerator centre exists in the medulla which may influence the sympathetic control of the heart. The sympathetic ganglia are influenced by the same drugs as the vagus ganglia and in similar manner. The sympathetic endings are stimulated by Adrenaline, Ephedrine, Amphetamine, Ergotoxine, and Cocaine.

(*c*) INTRINSIC NEURO-MUSCULAR MECHANISMS.—The excitability of the **sino-auricular node** is *stimulated* by Caffeine, Adrenaline and Thyroid; and it is *depressed* by peripheral vagal stimulants or cholinergic drugs, by Digitalis, Strophanthus (Ouabain) and Squill acting indirectly through the vagus centre, and by Quinidine. The conductivity of the **auriculo-ventricular bundle of His** is *depressed* by Digitalis, Strophanthus and Squill. The **cardiac muscle** itself is *stimulated* in its excitability, contractility and tone by

Digitalis, Strophanthus, Squill and Caffeine, and also by Calcium and Barium, but these last two alter the curve of the contractions. *Depressants* of the cardiac muscle are principally Chloroform, Chloral Hydrate, toxic doses of other organic hypnotics and Quinidine. Quinidine lengthens the refractory period and reduces the conductivity of cardiac muscle.

(*d*) THE CORONARY CIRCULATION.—An efficient coronary circulation is of primary importance for the nutrition of the heart. The coronary arteries are dilated by the sympathetic and, therefore, by Adrenaline, Ephedrine, Amphetamine and Methylamphetamine. By a direct action on the muscle, Nitrites for a short time and Caffeine, Theobromine and Theophylline for longer, dilate the coronary vessels. Digitalis directly constricts the muscle of the coronary arteries but, by prolonging the cardiac diastole, it increases the blood-flow through them; Posterior Pituitary Extract also constricts the coronary arteries.

(*e*) INDIRECT CARDIAC STIMULANTS AND DEPRESSANTS.—Moderate sensory stimuli such as irritation of the fifth nerve with Ammonia, or of the gastric mucosa by Alcohol and carminatives, or cold bathing, reflexly accelerate the heart. Conversely, powerful and prolonged sensory stimuli, such as very irritant purgatives or emetics, slow and weaken the cardiac contractions. Weak alcoholic beverages and Glucose act as nutrients to the cardiac muscle.

Rest is a most important means of diminishing the blood-pressure and the work of the heart, while muscular exercise increases both factors. Rest in bed reduces the heart's work to a minimum; and from this stage muscular exercise may be increased gradually, by massage, passive movements and resistance exercises in bed, to walking, gradual hill-climbing and outdoor games.

3. *The arteries.*—The arteries may be influenced through the vaso-motor centre, or locally through the terminations of the vaso-constrictor nerves, or by an action on the muscular coat itself.

The vaso-motor centre can be stimulated directly, and blood-pressure increased in animals but seldom in man, by Digitalis, Strophanthus, Strychnine and Cocaine; Nikethamide and Leptazol increase pressure in man. The *centre is depressed* by Chloroform, Chloral Hydrate, the Barbiturates and by large doses of Alcohol.

The *vaso-constrictor sympathetic ganglia* are stimulated and later depressed by Nicotine and Lobeline. The *vaso-constrictor nerve endings*, or myo-neural receptors, are powerfully stimulated by Adrenaline, the natural hormone, while Ephedrine and Amphetamine prolong its action by inhibiting its destruction by amine-oxydases. Ergot (Ergotoxine) causes great vascular constriction by stimulating the vaso-constrictor endings; Ergotoxine paralyses the endings later. Adrenaline can also stimulate the vaso-dilator nerve endings; thus, if the vaso-constrictors be previously paralysed by large doses of Ergotoxine, Adrenaline will cause a fall in pressure.

The *muscle of the arteries is stimulated* and its tone increased by the Digitalis series, by Posterior Pituitary Extract, and by toxic doses of Lead and Barium salts. Amyl Nitrite, Octyl Nitrite, Sodium Nitrite, Glyceryl Trinitrate, and Papaverine relax arterial muscle and cause a considerable fall in pressure. Histamine also lowers blood-pressure because it dilates the arterioles and capillaries and increases the permeability of the capillary endothelium. Nicotinic Acid dilates the superficial vessels. Digitalis dilates the renal vessels, but this effect is probably only a sequel to the improved circulation.

Local vascular alterations.—The size of the small arteries may be modified by local means. Thus the application to wounds or mucous surfaces of Adrenaline, which stimulates the vaso-constrictor receptors, produces constriction of the superficial vessels, blanching of the part and arrest of bleeding. Ephedrine, Amphetamine and Cocaine, by delaying the oxidation of Adrenaline, have similar local action. The application of cold will reflexly diminish local circulation for a time; and both Tannic Acid and metallic astringents may constrict the superficial vessels by forming round them an albuminous precipitate.

The *arterioles may be dilated*, and the local circulation augmented, by the application of warmth to the part in the form of poultices, or by the use of counter-irritants and rubefacients—Mustard, Volatile Oils, etc. Massage and muscular movement also increase the local circulation; and by suction tubes or "dry cupping" we may induce local congestion, which promotes diapedesis of leucocytes.

4. *The capillaries.*—The capillary circulation is largely dependent on the calibre of the arterioles and on the venous pressure, but the size of the capillaries is also constantly and independently changing by contraction or relaxation of the endothelial cells. Excess of carbon dioxide, or lactic acid, leads to their dilatation;

hence the capillary lumen will be regulated by the oxygen need of the tissues. Continued deficiency of oxygen supplied and blood stagnation will increase capillary permeability and lead to dropsical exudations. An intradermal injection of Histamine causes (1) by direct action, a local capillary dilatation; (2) by an axon reflex, dilatation of the surrounding arterioles; and (3) increased capillary permeability and the formation of a wheal. This effect is comparable with that produced by local sensory irritants, e.g. rubefacients, etc., which act, in part, by exciting local formation of histamine. Increased venous pressure causes stagnation of capillary circulation, with consequent exudation of fluid into the tissues. Posterior Pituitary Extract and Adrenaline cause contraction of the capillaries, and Posterior Pituitary Injection has proved useful in conditions of capillary paralysis.

5. *The veins.*—Digitalis has been found to reduce venous tone and pressure. Venesection is a rapid and valuable means of decreasing venous pressure which may embarrass the right auricle. Indirect measures, such as exercise and massage of the muscles, increase the venous return and are, therefore, useful in circulatory failure.

THERAPEUTICS

The rational principles which should guide the therapeutist in the treatment of disorders and diseases of the heart and blood-vessels can be illustrated sufficiently by a few examples.

1. **Circulatory disturbances,** which occur although the heart and vessels are healthy, require treatment of their underlying causes. Thus *faintness, palpitation* or tachycardia may be (1) of nervous origin and will respond to treatment by a reflex diffusible stimulant and subsequent sedatives such as Bromides or Phenobarbitone; (2) of anæmic origin, when hæmatinics are indicated; or (3) due to flatulence, which can be relieved by carminatives. When fainting or minor circulatory (vaso-vagal) collapse occurs, the most useful reflex stimulants are Ammonia vapour inhaled from Ammonium Bicarbonate (Smelling Salts), a tablespoonful of brandy or whisky, or 60 min. of Spiritus Ammoniæ Aromaticus or Spiritus Ætheris, each diluted with water and taken as a draught. If fainting attacks are recurrent, Ephedrine Hydrochloride or Methylamphetamine Sulphate orally in small doses may be successful preventives. In severe circulatory collapse an intramuscular injection of 0·3 Mil (5 min.) of Injectio Adrenalinæ, of 20 mg. (1/3 gr.) of Methylamphetamine Sulphate or of 0·25 G

(4 gr.) of Pholedrine Sulphate may be essential; or, if respiratory weakness is associated with the circulatory failure, a direct medullary stimulant, such as Picrotoxin, Nikethamide or Leptazol may be required. If the collapse be due to hæmorrhage, blood transfusion or Ringer's Solution intravenously will be necessary to restore the blood-volume and pressure.

2. **Valvular disease** of the heart following upon rheumatic endocarditis, etc., does not in itself require drug treatment. The diet should be nutritious and digestible in order to prevent cardiac disturbances from flatulent distension of the stomach or colon; mild purgatives assist in preventing this.

If compensation is perfect, drugs may do harm instead of good. Valvulotomy is as yet experimental; therefore rational treatment should be directed to avoiding any strain upon the heart, so that the reserve power possessed by the cardiac muscle is conserved. In valvular disease, physical exertion must be restricted to that amount which will not cause respiratory or cardiac distress and the patient must be cautioned against over-exertion. If cardiac or respiratory distress suggests that the myocardium is failing, rest, including freedom from worry or anxiety, is essential in proportion to the severity of the symptoms. Small doses of Digitalis may be given to slow and strengthen the beat.

The treatment of **cardiac failure in valvular disease** involves first the reduction of the peripheral resistance and intraventricular pressure by means of complete rest. The patient is confined to bed in the posture—usually with the shoulders raised—that affords him the most relief and enables him to sleep. Digestion is commonly impaired owing to venous congestion of the abdominal viscera or to over-feeding with fluids, and the resulting flatulence has a deleterious effect on the heart; small amounts of attractive nutritious solids given at regular intervals constitute the best diet, and fluids should be taken between and not with meals. The intake of salt should be reduced; tea and coffee—especially if the patient is sleepless—alcohol and other fluids may have to be restricted in order to prevent dropsy.

The objective which governs the medicinal treatment of cardiac failure is the restoration of an efficient circulation. Digitalis is of most service in a failing heart associated with rapid pulse, breathlessness and dropsy. Digitalis is worthy of trial in all cases of cardiac failure, provided that its use is continued only if—and as long as—it is found to improve the circulation. The total effective dosage necessary in the body of Tincture of Digitalis for full digitalization is 0·15 Mil (2¼ min.) per lb. body weight, i.e. 20 Mils (300 min.) for a 10-stone person, and from 1 to 1·5 Mil (15 to 22 min.) is destroyed or excreted daily by the body. With doses of 1 to 1·3 Mil (15 to 20 min.) every four or six hours, full effects will not, therefore, develop until after four or six days: but, if some action is desired within six hours and a full effect within twenty-four hours 10 Mils (150 min.) should be given at once and this dose halved every six hours; treatment is then continued with doses of from 1·3 to 2 Mils (20 to 30 min.) twice or thrice daily for maintenance according to the needs of the patient.

If the powdered leaf (Digitalis Præparata) as tablets is used, 0·1 G (1½ gr.) corresponds with 1 Mil (15 min.) of the Tincture, so that for full digitalization with it 2·1 G (32 gr.) is required; of it, 0·1 to 0·15 G (1½ to 2¼ gr.) is destroyed or excreted daily.

In urgent cases, an oral dose of 1·5 mg (1/40 gr.) or intravenous injection of 0·5 to 1 mg (1/120 to 1/60 gr.) of Digoxin will act within one hour or ten minutes respectively; or Ouabain, 0·12 to 0·25 mg (1/500 to 1/240 gr.) may be given intravenously. When the effects of these powerful glycosides begin to decline, an oral maintenance dosage with Digitalis or with Digoxin Tablets is arranged to achieve the maximal benefit.

Slowing of the diseased heart by Digitalis consists in lengthening of diastole, central vagus stimulation probably retarding the rhythmogenic stimuli; the longer diastole ensures better recuperation of the ventricular muscle and its improved nourishment through the coronary arteries; as a result, the beat immediately following a lengthened pause is stronger. Digitalis also benefits the failing heart by increasing directly the tone and contractile force of its muscle, and, by improving the force and volume of the pulse, it causes the disappearance of œdema and breathlessness. Digitalis does not increase the blood-pressure in man. If Digitalis is not well tolerated, Tincture of Strophanthus may be substituted.

Recent work indicates that the cardiac glycosides may produce their beneficial effects by (1) reducing venous tone and pressure, this action in "high-output" failure will lower the cardiac output whereas in "low-output" failure it will raise the cardiac output; (2) increasing the cardiac muscular force in certain types of failure, an action possessed more by Ouabain than by Digoxin (*see* p. 234).

Diuresis, due to the improved renal circulation, generally commences about the third day of Digitalis therapy in congestive cardiac failure and results in the disappearance of œdema. The amount of urine passed is large and of low specific gravity; if albuminuria has been present, this usually diminishes. If moderate œdema persists, Theophylline Ethylenediamine, Theobromine and Sodium Salicylate or Caffeine may be given as diuretics along with the maintenance dose of Digitalis. If œdema be severe, intramuscular or intravenous administration of Injectio Mersalyli 0·5 to 2 Mils (8 to 30 min.) should be employed; its diuretic action may be enhanced by giving Ammonium Chloride by mouth for some days previously; this treatment is inadvisable if nephritis be present.

Palliative treatment.—Cardiac pain, anxiety and sleeplessness decline as cardiac failure yields to treatment. But precordial pain may require relief by local application of hot-water bottles or ice bags; or by cerebral sedatives, such as Opium, which is of the greatest value because it does not influence the heart, although it has the disadvantage that in large doses it depresses the respiratory centre and is also constipating. Morphine Hydrochloride or Sulphate, 8 to 20 mg (1/8 to 1/3 gr.) is usually given either orally or hypodermically. Papaveretum, Pethidine, Disephonine and Heptalgin are alternative anodynes. Paraldehyde is a safe although unpleasant hypnotic for cardiac cases; Carbromal and Barbitone are very effective, while Bromides are useful to relieve anxiety and restlessness; Chloral Hydrate may also be used as a hypnotic in heart diseases; its depressant action on cardiac muscle is probably overrated.

Respiratory distress may be relieved by inhalations of Oxygen containing 5 per cent. Carbon Dioxide, or, if bronchitis is present, by expectorants such as Ammonium Bicarbonate, Potassium Iodide, and Squill; but dyspnœa, hæmoptysis, cough, and symptoms of pulmonary congestion usually improve rapidly under the influence of rest and Digitalis, although venesection may have to be employed when pulmonary congestion is severe. When recovery from cardiac failure has occurred, graduated exercises carried out against moderate and increasing resistance are of value provided their effects on the pulse are carefully controlled.

In **cardio-vascular syphilis,** antisyphilitic treatment should be instituted cautiously: Potassium Iodide and Bismuth are used initially and daily dosage with Penicillin in oil-wax suspension or as Procaine-Penicillin commenced with 30,000 Units and gradually increased to full dosage with a total of 6 mega-Units. The Organic Arsenicals are contra-indicated if the disease is advanced.

3. **Rhythmic irregularities.**—In *auricular fibrillation* Digitalis is of remarkable value; it is usually administered as Tincture of Digitalis or as Tablets of Digitalis Præparata or of Digoxin. Digitalis should be given in dosage sufficient to slow the pulse, and the daily dose then adjusted so as to avoid toxic symptoms. The optimum dose having been found, it may have to be kept up during life. It acts by reducing the conductivity of the bundle of His, and thus prevents a proportion of the auricular impulses from reaching the ventricle; Digitalis does not check the fibrillation of the auricle. In urgent cases, Digoxin, when given orally, 1 to 1·5 mg (1/60 to 1/40 gr.), in tablet form begins to slow the heart in one hour and attains its maximal effect in six hours, thereafter a maintenance dose of 0·25 mg (1/240 gr.) once or twice daily may be sufficient; Digoxin cannot be given hypodermically as it is irritant, but if injected intravenously, 0·5 to 1 mg (1/120 to 1/60 gr.) it begins to act in 5 to 10 minutes and develops its maximal effect in one or two hours. Ouabain given intravenously also acts in a few minutes. If a Digitalis preparation causes much nausea, Tincture of Strophanthus, which is less irritant, may be substituted. Quinidine Sulphate, by increasing the refractory period of the auricular muscle, may in 50 per cent. of cases restore normal rhythm in auricular fibrillation (*see* p. 240), but this drug may cause cardiac failure in a weakened heart; again, in cases where fibrillation has existed for some weeks, or in recurrent attacks, restoration of a normal auricular beat may detach emboli which have formed in the auricle. Quinidine is most useful in recent cases of fibrillation after the heart has been brought under the control of Digitalis.

In *auricular flutter* Digitalis may induce heart-block and thus slow the ventricular rate; it may then convert the flutter into auricular fibrillation, and this may suddenly cease just after the drug is withdrawn. *Sinus arrhythmia* demands no treatment. *Extrasystoles*, when present in neurotics, may be treated with Bromides or Phenobarbitone; the condition otherwise is of minor significance, and is not readily amenable to drug treatment. *Tachycardia*, acute or persistent, demands treatment of its cause. If it is due to auricular fibrillation, Digitalis or Quinidine is indicated; if it is due to thyrotoxicosis, Thiouracil or Lugol's Iodine should be given. *Paroxysmal tachycardia*, brought on by dyspepsia, constipation or mental worry, is treated by correction of these disorders with a gastric sedative, purgative, or Bromides, respectively. If it is due to abnormal rhythmic stimuli and cardiac failure occurs. Digitalis should be tried; but, by increasing the parasympathetic control, Acetyl-β-methylcholine, 10 to 20 mg (1/6 to 1/3 gr.) subcutaneously, or Carbachol, 0·25 to 0·5 (1/240 to 1/120 gr.) subcutaneously, act rapidly and successfully in many cases where the abnormal focus is in the auricle.

The *Adams-Stokes syndrome* (heart-block) would obviously be increased by Digitalis. Heart-block is usually partial, with intermissions of a complete block which give rise to sudden attacks of syncope (Stokes-Adams attacks). Atropine may sometimes be of value to paralyse the vagus, but usually only the auricular rhythm is accelerated. Injectio Adrenalinæ, 5 to 15 min. hypodermically and Ephedrine Hydrochloride, 1/2 gr. at eight-hourly intervals, have proved very successful in some cases of heart-block. If the origin be syphilitic, Iodides should be tried. In complete block where the ventricle is contracting at its own rhythm, Digitalis is not contra-indicated and will often do good if the heart is failing.

Angina pectoris or *angina of effort* should be treated during the attack by inhalation of Amyl or Octyl Nitrite to dilate the coronary arteries, and an injection of Morphine is frequently required also to relieve the intense pain. In the intervals between seizures, Tablets of Glyceryl Trinitrate for sublingual absorption are usually employed to avert the coronary spasm and lower blood-pressure; Sodium Nitrite is less valuable. Potassium Iodide, Theobromine Sodium Salicylate, Theophylline Sodium Acetate, or Theophylline Ethylenediamine are sometimes of service in these cases.

Coronary Thrombosis is treated by immediate absolute bed-rest, warmth to combat initial shock and Morphine, 20 mg (1/3 gr.) to relieve the intense pain, the Morphine may be repeated orally, if necessary, in an hour or two and is withheld only if dyspnœa occurs. Heparin and Dicoumarol have been advised but are best reserved for cases of spread and their effects must be watched carefully, Nitrites should not be used.

Subacute bacterial endocarditis requires treatment by 500,000 Units of Penicillin in divided doses daily for at least twenty-eight days; this controls the infection (Streptococcus viridans) but the patient must be kept under observation for relapses.

4. **Arterial diseases.**—*Arterio-sclerosis* should be treated mainly by arranging a low but nutritive diet with reduced protein and salt; alcohol and tobacco should be forbidden. Purgatives and diuretics are given to decrease the blood-volume. Potassium

Iodide or small doses of Thyroid sometimes prove of value in retarding the degenerative process. *High arterial tension* is treated in urgent cases by Amyl Nitrite inhalations, in less urgent cases by Tablets of Glyceryl Trinitrate, Sodium Nitrite, Papaverine, Tetraethyl-ammonium bromide, Iodides, Theobromine Sodium Salicylate, or Theophylline Ethylenediamine but their effects are transitory. Potassium Thiocyanate has a longer action but its dosage has to be carefully controlled (*see* p. 254). Nicotinic Acid which dilates the skin vessels has been used for chilblains and angio-neurotic œdema. In patients with hypertension, gentle exercise only is allowed, and warm baths ordered, followed by early retirement to bed.

Peripheral arterial disease can be most successfully combated when its effects are mainly due to spasm of the muscular coat. Such spasm is temporarily relaxed by Carbachol and Tetraethyl-ammonium Bromide. The anti-adrenaline (sympatholytic) compounds Priscol (benzylimidazoline hydrochloride), Dose, orally: 10 to 50 mg (1/6 to 3/4 gr.) and Dibenamine (dibenzyl-β-chloro-ethyl-amine) hydrochloride, which dilate peripheral vessels, have given promising results in Raynaud's disease. Dibenamine is given intravenously in doses of 4 to 6 mg per kg body weight up to a total of 0·5 G, but must be diluted in order to obviate venous thrombosis. It is said to block sympathetic ganglia for 24 to 96 hours. The operation of sympathetic ganglionectomy is more lasting in its effects. Narrowing of the arteries due to atheroma is countered by passive vascular exercises, designed to open up collateral vessels.

5. **Venous Disease.**—The veins of the lower limbs often become varicose; this condition is treated by elastic support, by ligature or by the localized injection of solutions which cause an inflammatory sclerosis of the vein, e.g. Injection of Ethanolamine Oleate, 2 to 5 Mils of 5 per cent., causes no pain or perivenal reaction if it escapes; or 0·5 to 5 Mils of Injectio Quininæ et Urethani which is also used for hydrocele. Internal hæmorrhoids are sclerosed by injections of Phenol 5 per cent. in Olive Oil.

CHAPTER IX

THE RESPIRATORY SYSTEM

PHARMACOLOGY

THE movements of the chest are governed by the *respiratory centre* in the medulla, which receives afferent impressions from the inspiratory and expiratory vagal fibres and from the aortic and carotid bodies; it transmits efferent impulses by the vagus to the bronchi, and by the intercostal and phrenic nerves to the chest-muscles and diaphragm. Normally the vagus nerve controls the rate of respiration while the carbon-dioxide tension of the blood controls its depth. The respiratory centre can be influenced, in addition, by impulses received from the cerebrum; and also reflexly by impressions conveyed through all sensory nerves, but particularly those from the nose and mouth. The centre is stimulated by increase of body temperature, e.g. in fever.

The *bronchi* are supplied by the vagus with *motor fibres*, which constrict the bronchial muscles; with *secretory fibres* to the bronchial glands, and also with *sensory fibres* that convey impressions which excite the cough reflex. The *sympathetic* provides the bronchial muscles with inhibitory or dilator fibres and the glands with inhibitory fibres.

The functions of the respiratory organs can be modified in many different ways:—

1. **Physical Properties of Air.**—The physical condition of the respired air may be modified in regard to (*a*) *temperature*, by artificial regulation of the warmth of the room or by selecting a suitable climate; (*b*) *moisture*, by increasing the water vapour in the inhaled air by means of steam kettles in the room or steam inhalers, or by residence in a dry or moist climate; (*c*) *pressure*, by residence at high altitude, which increases the depth and frequency of respiration and causes compensatory increase in the hæmoglobin and red cells owing to the lowered oxygen tension of the air; (*d*) *composition*, by the inhalation of Oxygen by means of a B.L.B. mask or tent to increase the oxygen absorbed by the plasma; and (*e*) *purity*, by transferring from town to mountain or

seaside resorts where the air is freer from dust particles and bacteria.

2. **Chemical Constitution of Air—Oxygen and Carbon Dioxide.**—The respiratory centre, through the aortic and carotid bodies, is extremely sensitive to any increase in the *carbonic-acid tension* (increased H-ion concentration) of the plasma; this stimulates it and causes increased depth of respiration, as occurs in muscular exercise in order to remove the excess of carbon dioxide and increase the intake of oxygen. Slight changes in the H-ion concentration are resisted by the "buffer salts" of the plasma. It responds similarly to decreased oxygen tension, but only when this falls much below the normal.

This self-regulating mechanism may, however, be upset by *deficiency of oxygen* (anoxæmia). This may arise from (1) insufficient oxygen pressure in the blood, as in rarefied atmospheres and in pulmonary consolidation or occlusion of alveoli by mucus, etc.; (2) lack of hæmoglobin, as in anæmia and in carbon-monoxide, nitrite, or sulphonal poisoning; (3) impairment in circulation, when the blood-flow through the tissues is slower, e.g. in chronic heart disease and in hæmorrhage, shock and syncope.

The respiratory centre responds immediately to lack of oxygen by increased breathing and, when this is associated with excess of carbon dioxide, the condition is automatically relieved. But if there be no excess of carbonic acid, the increased breathing eliminates more carbon dioxide, so that the H-ion concentration of the blood is reduced (*alkalosis*). The result is two-fold: (*a*) less oxygen is dissociated from oxy-hæmoglobin in the tissues, and (*b*) the respiratory centre is deprived of its normal stimulus; thus oxygen-want (**anoxæmia**) is produced, and yet the venous blood may be bright red in colour and there may be no dyspnœa.

Slight but persistent anoxæmia leads rapidly to fatigue of the respiratory centre; hence it is a symptom demanding immediate relief. Acute anoxæmia—sudden arrest of oxygen supply—as in drowning, is soon fatal; but, if it be only of short duration, the tissues soon recover from the defect.

The amount of oxygen which dissolves in the plasma is proportional to the oxygen-tension in the alveolar air, which contains about 14 per cent. of Oxygen, and upon this fact depends the value of Oxygen inhalations, which can increase the normal amount (0·3 per cent.) in solution by the plasma up to 3 per cent. Thus Oxygen inhalations can overcome an anoxæmic crisis.

The inhalation of Carbon Dioxide, by increasing its tension in the arterial blood, increases the depth of respiration; 3 per cent. of Carbon Dioxide in the inspired air will double, and 5 per cent. treble, the depth of respiration. Carbon Dioxide is therefore an effective means of restoring or improving respiration but, as anoxæmia is also usually present when respiration is deficient, inhalations of a mixture of Carbon Dioxide 5 per cent. with Oxgen 95 per cent. are more valuable. Inhalations of Carbon Dioxide are a useful means of alleviating persistent hiccough.

3. **The Pulmonary Circulation.**—The pulmonary circulation is dependent partly on the movements of inspiration and expiration but is mainly governed by the state of the general circulation. As there are few vaso-constrictor nerves in the lungs, Adrenaline and Ephedrine have no useful effect on pulmonary vessels.

4. **The Bronchioles.**—(*a*) *Ciliary action.* The movements of the bronchial cilia, which are directed towards the removal of mucus, etc., are accelerated by Oxygen; their movements are decreased by Carbon Dioxide, by Ether and Chloroform vapours.

(*b*) The *afferent or sensory nerves* of the bronchi are *stimulated* by the inhalations of cold and dry air, irritant gases, Ammonia, Tobacco, and Nitre fumes, or by Volatile Oils when inhaled or excreted by the mucous membrane; reflexly, these agents stimulate the respiratory centre, and so increase the thoracic movements, and excite cough. They are *depressed* or soothed directly by warm and moist air, by sprays of Cocaine Hydrochloride (1/2 per cent.) and by inhalation of dilute Chloroform vapour, and reflexly by warm applications to the chest wall. Pain or sensations of irritation arising from the bronchioles may be mitigated by these means, or can be checked by a central anodyne, Morphine.

(*c*) *The bronchial glands.*—**Expectorants** are drugs which *increase and liquefy the bronchial mucous secretion* and thus facilitate its expulsion by the cough reflex. Expectorants are classified according to their mode of action: (1) Drugs which irritate the sensory vagal endings in the stomach produce reflexly through the vagus centre an increased and more watery secretion of bronchial mucus. This action is produced by small doses of emetics, such as Ammonium Bicarbonate, Ipecacuanha, Squill, Senega, and Potassium or Sodium Antimonyl Tartrate, as well as by Volatile Oils, e.g. Camphor, etc. (2) Apomorphine, which stimulates the vomiting centre, has, in small doses, a brief expectorant action; (3) Drugs which stimulate the bronchial glands during their excretion by the mucosa. Iodides produce a profuse watery secretion of bronchial mucus by a direct action on the secretory cells, and the Volatile Oils, oleoresins, and balsams, e.g. Camphor, Benzoin, and Balsams of Peru and Tolu, act as expectorants, partly by mild irritation of the bronchial mucous membrane during their excretion through it. It should be noted, however, that these Volatile Oils irritate the gastric mucosa and thus have a reflex expectorant action also. (4) Drugs which stimulate the cholinergic secretory vagal endings, such as Pilocarpine and Physostigmine, produce a profuse flow of mucus but, even as adjuvants in small doses, these drugs, because of their cardiac action, are unsuitable as expectorants.

The *bronchial secretions can be diminished* by: (1) Drugs which paralyse the secretory vagal endings, e.g. Atropine, Hyoscyamine and Hyoscine; (2) Drugs which briefly stimulate and then paralyse the secretory ganglia, e.g. Lobeline, Nicotine, and Coniine; and (3) by Morphine, which acts centrally and reduces bronchial mucous secretion.

(*d*) *Bronchial muscle.*—The size of the bronchioles can be influenced by drugs which modify the tone of the bronchial muscle. The *bronchial muscle is contracted* by: (1) Stimulants of the vagal endings (cholinergic drugs), e.g. Physostigmine, Neostigmine, Pilocarpine, Muscarine, Arecoline, Carbachol and Acetylcholine; (2) Stimulants of the vagal ganglia, e.g. early action of Lobeline, Nicotine, and Coniine; (3) Stimulants of the muscle directly, e.g. Pituitrin, Histamine, or large doses of Morphine. These actions have no therapeutic applications.

Very important are the means—so-called **respiratory antispasmodics**—by which *the bronchial muscle can be relaxed*, namely: (1) Drugs which reduce the irritability of the sensory vagal endings in the bronchi, such as sprays containing Cocaine or inhalations of water-vapour; (2) Drugs which paralyse the vagal endings in the muscles, or are anti-cholinergic, namely the Atropine series—Belladonna, Stramonium, and Hyoscyamus; (3) Drugs which paralyse the vagal ganglia, e.g. Lobelia and Nicotine; (4) Drugs which stimulate the sympathetic endings and thus relax bronchial muscle, namely Adrenaline, Ephedrine and Amphetamine; (5) Drugs which directly relax the muscle, such as Amyl Nitrite and Glyceryl Trinitrate, Theophylline Ethylenediamine and Theamine; or lastly, (6) central respiratory sedatives, such as Chloroform, Opium, Morphine, Diamorphine, or Codeine.

5. **The Respiratory Centre.**—Increased carbon-dioxide tension (increased H-ion concentration) in the blood is, through the

aortic and carotid bodies, the most important central stimulant, but the respiratory centre may be influenced through other channels. Its activity may be *reflexly increased* and the rate, and possibly depth, of breathing augmented by irritation of sensory nerve endings, for example of the fifth cranial nerve in the nose by Ammonia; of the cutaneous nerves by flicking with towels, application of cold as in the cold bath or douche; or of the vagus in the stomach by Alcohol, Volatile Oils, etc. A reflex *sedative* action on the respiratory centre is produced by warm baths, or warmth applied to the chest in the form of poultices and fomentations, or by counter-irritant and anodyne liniments, e.g. of Camphor, Chloroform and Turpentine. When the centre is in an excited state from anxiety, Alcohol steadies and slows respiration by depressing the higher cerebral areas.

The respiratory centre is *stimulated directly* by Carbon Dioxide, Strychnine, Caffeine, Nikethamide, Leptazol, Picrotoxin, Lobeline, Atropine and Cocaine. The centre is *depressed* directly by Morphine, Codeine, Diamorphine, and by large doses of Atropine, organic hypnotics and general anæsthetics. It must be observed, however, that before Morphine depresses the respiratory centre, it depresses the closely associated *cough centre* and thus abolishes the cough reflex.

6. **The Cough Centre**, which is closely connected with the respiratory centre, acts reflexly in response to irritation of the sensory vagal endings in the bronchioles.

The *cough reflex can be increased* and coughing stimulated (1) by medullary stimulants, e.g. Strychnine and Caffeine; (2) by peripheral stimulation of the sensory vagal endings in the bronchioles, e.g. by inhalation of the vapour of Ammonia or of Volatile Oils, etc., such as Eucalyptus, Thymol, Tinctura Benzoini Composita; and (3) indirectly, by the use of expectorants, which increase and liquefy the bronchial mucus.

The *cough reflex can be depressed* and coughing diminished by (1) medullary depressants, e.g. Morphine, Diamorphine or Codeine, the last having the advantages that it does not cause constipation or habit; (2) peripheral sedatives of the vagal endings, such as warm or counter-irritant applications to the chest, which act reflexly, or inhalation of warm water-vapour, or a spray containing Cocaine Hydrochloride (1/2 to 1 per cent.) which is occasionally necessary to check cough and facilitate the removal of a foreign body in the bronchus; (3) parasympathetic depressants, e.g. Atropine, which reduce or arrest bronchial secretion. Drugs which allay cough are sometimes spoken of as respiratory sedatives.

It is common to use expectorants in combination with small doses of respiratory sedatives in order to allay the discomfort of coughing. Examples are the Tinctura Opii Camphorata, and Pulvis Ipecacuanhæ et Opii of the Pharmacopœia. A Bromide or an organic hypnotic is often prescribed with expectorants in preference to Opium.

7. **Pulmonary Antiseptics.**—In pulmonary infections by the pneumococcus and other sensitive organisms, Penicillin and the Sulphonamides—Sulphadimidine, Sulphamerazine, Sulphadiazine or Sulphathiazole—have proved to be specific curative agents and are given initially in large "loading" doses with subsequent doses to maintain an adequate inhibitory blood concentration. In pulmonary tuberculosis, Streptomycin is valuable in some types of the disease and as a prophylactic in chest surgery (*see* p. 419). A slight antiseptic and deodorant action on the bronchial mucosa can be attained by giving antiseptic substances which are partly excreted through the bronchial glands; these are Creosote, Volatile Oils and Balsams. The small amounts of these which are excreted do not kill bacteria but may inhibit their growth. These drugs may also be given by inhalation in the form of a warmed vapour or spray.

8. **The Respiratory Functions** may be improved generally by outdoor recreations in loose clothing, and by systematic respiratory exercises—"breathing exercises."

THERAPEUTICS

The rational treatment of respiratory disorders is founded upon the preceding principles which are modified to suit particular diseases.

Cough.—This reflex symptom may be purely neurotic or may originate from laryngeal, bronchial, pulmonary or pleural inflammation, and from malignant disease. Nervous cough responds to psychotherapy and the administration of Phenobarbitone. Pharyngeal or laryngeal cough may require the use of Penicillin, or antiseptic, lozenges or inhalations of warm water vapour containing antiseptic Volatile Oils. Bronchial catarrh with cough is a frequent sequel of common colds, influenza, and other fevers; it is effectively treated by prescribing reflex expectorants, e.g. Ammonium Bicarbonate, Tinctura Ipecacuanhæ, or Tinctura Scillæ along with small doses of Tinctura Opii Camphorata.

With these, Iodides, which directly increase the secretion of the bronchial glands, may be prescribed. The painful cough of pleurisy can often be relieved by the application of adhesive plaster to the area, but to secure sleep at night Pulvis Ipecacuanhæ et Opii or a hypodermic injection of Morphine may be necessary. Cough following broncho-pneumonia or lobar pneumonia requires to be encouraged by reflex expectorants, e.g. Ammonium Bicarbonate or Squill, and the cough reflex may require to be stimulated by small doses of Strychnine. In the resolution stage of pneumonia, Opium or Morphine should be avoided as they depress the respiratory and cough centres. In fact in all pulmonary conditions where the sputum is profuse, Opium should be withheld.

A slight antiseptic action on the bronchial mucosa and a stimulation of the secretion may be obtained by inhalation of the vapour of hot water, to which Creosote, Tinct. Benzoini Co., Camphor, Thymol, or other Volatile Oil has been added, or of fine sprays containing Volatile Oils; these are of value if the sputum has become purulent.

Dyspnœa.—The symptoms of *obstructive* dyspnœa, e.g. in bronchial affections, indicate the necessity for increased freedom and activity of respiration—of assisting hyperpnœa by admitting as much air as possible into the chest. The air of the sick-room must be fresh, warm and moist, and additional Oxygen may be necessary. By the use of a double nasal catheter, the Oxygen in the alveolar air (14 per cent.) can be increased to about 40 per cent. with a flow of 6 litres per minute; while, by means of a B.L.B. mask, this amount can be raised to nearly 90 per cent. with a flow of 6 litres of Oxygen per minute. Specially constructed Oxygen tents are sometimes used. The muscles of respiration must be free from restraint by heavy bed-clothing, the shoulders raised, and the back firmly supported so as to permit free movement of the abdomen. By suitable diet and regular purgation, the stomach and bowels are freed from flatulence, which would impede the movements of the diaphragm, and the reserve strength of the heart must be spared by rest. Dyspnœa with cyanosis (i.e. carbonic-acid excess) shows that the circulation is failing and circulatory stimulants are indicated.

In **acute lobar pneumonia** the general treatment consists in keeping the atmosphere of the sick-room fresh at a temperature of 60° to 65° F., light but warm bed-clothes are provided and a pneumonia jacket to protect the chest without encumbering the movements. The diet should be fluid but highly nutritious; rest is essential to conserve the patient's strength and, in the early stages, it may be necessary to overcome restlessness and ensure sleep by giving Phenobarbitone or Morphine.

The choice of curative treatment lies between Sulphonamides and Penicillin, both of which are specific inhibitory agents against the pneumococcus. Sulphadimidine (Sulphamezathine), Sulphamerazine, Sulphadiazine and Sulphathiazole have about an equal bacteriostatic effect on the pneumococcus, but the acetyl derivatives of the first two are more soluble in urine, hence the risk of crystalluria is less; it is, however, wise to give adequate fluids and remote antacids even with them. Also, as the former two are less rapidly excreted, their concentration in the blood lasts longer, and dosage can be more widely spaced.

These Sulphonamides are given orally in 0·5 G tablets, which, when crushed and given in water, are less likely to cause nausea. Two initial "loading" doses of 3 to 4 G are best given at an interval of four hours, and, thereafter, day and night, maintenance doses of 1 G four-hourly (Sulphadiazine and Sulphathiazole), or six-hourly (Sulphadimidine), or eight-hourly (Sulphamerazine) are continued till the temperature falls and for a further two or three days. Tablets containing mixtures of Sulphonamides, e.g. *Sulphatriad*—Sulphathiazole and Sulphadiazine each 37 per cent. with Sulphamerazine 26 per cent.—are also used. If the patient is nauseated by oral dosage or is severely ill, intravenous injection of a soluble sodium salt of these compounds in doses of 1 to 2 G is successfully used to gain an immediate high blood concentration.

The Sulphonamides have the advantage that oral dosage is more convenient and less disturbing to the patient than repeated injections of Penicillin. Against this must be weighed their possible toxic effects (*see* p. 401) which are, however, less common with the above preparations than they were with Sulphapyridine. Sulphonamides would be inadvisable in patients who had formerly exhibited toxic effects from them, or who have impaired renal or hepatic functions.

Penicillin is given by intramuscular injection in the buttock or abdominal muscles in doses of at least 50,000 to 100,000 Units at four-hourly intervals during the day and, to avoid a night dose, 200,000 Units in the evening; or 200,000 Units at 6- or 8-hourly intervals in order to maintain a high blood concentration. To avoid frequent disturbance of the patient, the Injectio Penicillini Oleosa may be used, or Procaine-Penicillin with 2 per cent.

Aluminium Stearate in Arachis Oil, or Distaquaine, an aqueous suspension of Penicillin; these have a prolonged action by slowing the absorption of the Penicillin from the injection site, so that 300,000 Units daily may suffice. Penicillin may be used along with Sulphonamides in serious cases of pneumonia or is substituted when cases fail to respond to Sulphonamides.

Broncho-pneumonia, capillary bronchitis and severe acute bronchitis are treated on similar principles; in acute bronchitis, inhalations of Penicillin finely vaporized from 1 Mil containing 50,000 Units, and used four times daily, are of value.

The heart may be improved by prescribing Digitalis and, if the circulation shows signs of failure, Adrenaline, Methylamphetamine, or Atropine injections may be required. If the dyspnœa becomes complicated by cyanosis, inhalation of Oxygen through a B.L.B. mask is of great value, or the patient may be placed in an Oxygen tent, while the respiratory centre may be stimulated also by Caffeine or injections of Strychnine.

Spasmodic Asthma.—The treatment of an acute attack of asthma consists in the use of drugs which will dilate the bronchioles. Injectio Adrenalinæ, given hypodermically, often affords immediate relief and Ephedrine can be given simultaneously by mouth to retard the oxidation of Adrenaline and prolong its action. Isopropyl Adrenaline (Neo-epinine), 10 to 30 mg, given as a tablet to be held for absorption under the tongue thrice daily, is rapidly effective and obviates injections of Adrenaline. An injection of Atropine Sulphate to paralyse the vagal endings and an inhalation of Amyl Nitrite to depress the muscle are often valuable. In the intervals between attacks, Ephedrine, Belladonna or Stramonium may be prescribed. Sprays containing Atropine, Cocaine and Adrenaline often serve to ward off attacks. Theamin (Theophylline monoethanolamine) in doses of 0·2 G (3 gr.) is often of value and it may be given with Amylobarbitone in neurotic patients. As spasmodic asthma and hay fever may be allergic responses to an antigen, specific or non-specific Protein Therapy and Pollen Vaccine respectively may cure the complaint (*see* p. 456). The antihistaminic drugs, Anthisan, Benadryl and Antistin, usually relieve hay fever but are less successful for asthma.

The treatment of **pulmonary tuberculosis** depends on the extent of the lesions. Early cases improve on initial bed-rest, nutritious food and graduated exercise under sanatorium control. Collapse therapy or thoracic surgery is advisable in suitable cases. Streptomycin is the most valuable inhibitory drug at present; Dihydrostreptomycin is less liable to cause vestibular dysfunction but resistant strains also develop to it. Para-aminosalicylic acid is of value locally for tuberculous skin lesions and, by mouth, for systemic treatment of pulmonary cases, particularly in association with Streptomycin, because it postpones or inhibits the development of Streptomycin-resistant strains of M. tuberculosis (*see* pp. 411 and 419). Sulphetrone is also on trial but seems more effective for leprosy.

Respiratory failure arising from narcotic poisoning, anæsthetics, or other causes is treated by inhalation of Carbon Dioxide, 5 per cent., and Oxygen, 95 per cent.; and, in addition, stimulants of the medullary centre for respiration (Analeptics), such as Picrotoxin, Nikethamide, Leptazol, Strychnine, or Caffeine and Sodium Benzoate, should be administered by injection.

CHAPTER X

THE NERVOUS SYSTEM

PHARMACOLOGY

THE nervous system is built up of afferent, efferent and associating neurons. A stimulus applied to a sensory afferent neuron is conducted through a posterior root ganglion to the spinal cord where it may be reflected through a synapse to an efferent neuron and be transmitted as an excitory or inhibitory stimulus to a muscle; this is termed *reflex action.* Sensory impulses are normally co-ordinated to induce an excitory impulse in one motor neuron, say, that of a flexor muscle, and an inhibitory impulse in its antagonist extensor muscle (reciprocal innervation). The sensory stimulus is also conveyed by the sensory tracts of the cord to the sensory area of the cerebrum, there to be perceived, with peripheral reference, as pain, heat, etc., and to cause volitional impulses from the motor area so as to avoid recurrence of the painful stimulus. It is by reflex action that the majority of the functions of the body are regulated; many of these reflexes, e.g. cardiac reflexes, are beyond control by the intellect, while others, e.g. the automatic respiratory reflex, can to some extent be controlled by the intellect.

The *highest cerebral centres* are the seat of the intellect, memory, judgment, volitional and inhibitory will-power and emotions. The *intellectual area* is dependent for its information on the perceptive and sensory areas; from this information, memory stores knowledge derived from environment, instruction or experience, and upon these the intellect forms judgments and determines the will. *Consciousness* depends essentially upon the activity of the perceptive centres, and, if these be fatigued or depressed, sleep ensues and may be accompanied by fantastic dreams, since the intellect and judgment are deprived of the guidance of perception and its experience. It is possible that sleep may be induced by interruption of perceptive impressions at the thalamic level. The *perceptive centres* are those to which impressions derived from environment by the afferent nerves from the special senses of touch, taste, smell, sight and hearing are conveyed, while the *parietal sensory areas* are discriminative of these impressions and of pain. The perceptive and sensory areas may be common for a given sense, are not confined to one part of the cortex, and are in intimate nervous association with the other centres. The *motor area*, including that of speech, is influenced by sensory perception and governed by the intellect; therefore drugs which depress the intellect and its inhibitory control may lead to uncontrolled motor activity and speech. The *cerebellum* is concerned chiefly with equilibration and the co-ordination of muscular movement. It receives impressions from touch, vision, the orientation of muscles and the semicircular canals, all essential to the maintenance of equilibrium. The *basal ganglia* are essentially a cell station: the corpus striatum is a station on the path of the motor fibres; the hypothalamus contains the heat-regulating centre; the thalamus is a station for sensory neurons. In the *medulla oblongata* are situated the respiratory, vagus, vasomotor and vomiting centres. The efferent nerves to the viscera are derived partly from the medulla direct or through the cord (parasympathetic) and partly from the sympathetic chain. The viscera possess also intrinsic local ganglia acting automatically but controlled to varying degrees by the medullary centres.

The action of drugs is often selective upon a particular part of the central nervous system as the following survey will illustrate.

1. SENSATION.—The perception of pain and to a lesser extent of touch and temperature can be influenced locally and centrally.

(i) *Drugs influencing sensation peripherally:*

(*a*) **Local sensory stimulants.**—This term is used for drugs which increase common sensibility or even excite pain. Most of them stimulate directly the *sensory receptors* in superficial tissues, e.g. heat, cold (for a time), and many drugs, including Iodine and Ammonia, Alcohol, Ether and Chloroform, when their vapour is confined, Volatile Oils, e.g. Turpentine, Camphor, Mustard. Mineral Acids and soluble metallic salts, which by forming albuminates liberate acid, as well preparations of Antimony and Arsenic, also irritate sensory nerves and cause severe pain if applied to raw surfaces or injected subcutaneously or intramuscularly.

The sensation of pain, due to local irritation and referred to the periphery, is partly a thalamic (crude) and partly a cerebral perception. Local stimulants, therefore, afford a means not only of increasing the local vascularity by an axon reflex, but also, through the cord, of improving muscular tone, and through the medulla of stimulating the circulatory and respiratory systems and, finally, of exciting the cerebral centres. Thus a cold plunge produces a sensation of cold referred to the part, rouses consciousness, and excites the respiratory centre to cause deeper breathing and accelerates the heart. *Local stimulants may, in fact, become reflex general stimulants.*

(*b*) **Local anæsthetics.**—The excitability of the sensory nerve terminations can be diminished until they are unable to transmit sensory impressions to the central nervous system. The drugs which have this effect are called **local anæsthetics**, which abolish sensation, or, if only pain be relieved, **local anodynes** or **analgesics**. A slight degree of local analgesia follows from subsequent paralysis of sensory endings if the action of local sensory stimulants is prolonged. This explains the relief of local pain by counter-irritant liniments or ointments which contain Turpentine, Camphor, Menthol, Thymol, Methyl Salicylate, Chloroform, Alcohol, etc., and the local anæsthetic effect of Aconite, Atropine, and Phenol. Superficial freezing, by paralysing the sensory endings, produces anæsthesia, and sprays of Ethyl Chloride are used to produce this effect; thawing is, however, painful. Warmth also reduces sensory excitability, therefore hot fomentations and poultices give considerable relief when applied over areas to which pain is referred from deeper-seated inflammatory disease, e.g. pleurisy. Gentle massage also diminishes the sensitiveness of the cutaneous receptors.

More important are the local anæsthetics which paralyse sensory endings and fibrils. Those which are absorbed by mucous membranes and act as *surface anæsthetics* are Cocaine, Cinchocaine, Butacaine, Amethocaine, Benzocaine, Orthocaine and Butyl Aminobenzoate. For *local injection*, Procaine, which is less toxic than Cocaine, is generally preferred but Cinchocaine, Butacaine, Amethocaine and Xylocaine may be used.

(*c*) **Trunks of mixed nerves** may be influenced so as to prevent the conduction of sensory (and even motor) impulses—regional anæsthesia (nerve-blocking). This is achieved by injecting around them solutions of Procaine, or Cinchocaine Hydrochlorides.

(*d*) **Transmission through the spinal cord** of sensory, and also motor, impulses may be checked. The injection is made into the lumbar subdural space of 2 Mils or 5 per cent. Procaine Hydrochloride in Normal Saline Solution; or of Amethocaine or Cinchocaine Hydrochloride in 0·066 per cent. strength in 0·5 per cent. Sodium Chloride (hypobaric for high anæsthesia) or in 0·5 per cent.

strength in 6 per cent. Dextrose (hyperbaric for low anæsthesia). The intraspinal dosage is usually 5 to 10 mg (1/12 to 1/6 gr.). Numbness and anæsthesia to touch and pain occur quickly; muscular relaxation and loss of reflexes follow. Spinal anæsthesia causes a considerable fall in blood-pressure.

(ii) *Drugs influencing sensation centrally:*

(*e*) The **perceptive centres** in the cerebrum are the first to be depressed by the action of the organic hypnotics, e.g. Paraldehyde, Chloral Hydrate, Sulphonal, and the Barbiturates. These, by rendering the cerebrum less excitable by external impressions, promote sleep.

(*f*) The **cerebral sensory area** is selectively depressed by Opium and its alkaloid Morphine, Pethidine, Disephonine and Heptalgin, to a lesser extent by Codeine and Diamorphine. These drugs relieve pain without materially depressing the intellect.

(*g*) The **thalamic cell station** on the path of the pain fibres is depressed by Acetylsalicylic Acid, Phenacetin, Phenazonum, and Amidopyrin, therefore these drugs can relieve mild degrees of pain without interfering with the cerebral functions.

(*h*) **General anæsthetics.**—Chloroform, Ether, Ethyl Chloride, Nitrous Oxide, Cyclopropane and Trichloroethylene, and also large doses of organic hypnotics, such as Paraldehyde, Bromethol, Pentobarbitone and particularly Thiopentone and Hexobarbitone, used as basal anæsthetics, produce a progressive depression of the perceptive, intellectual, sensory and motor centres and thus abolish consciousness and motor activity.

(*i*) The **special senses** can be influenced by drugs. Thus, Strychnine increases the sensitiveness of all special senses and in particular increases the field of vision for blue rays. Deafness and subjective noises are caused by over-dosage with Quinine and Salicylates; Streptomycin, given for a long period, causes serious vestibular dysfunction. Partial (amblyopia) or complete (amaurosis) blindness may be caused through optic neuritis from overdosage with Lead, Quinine, Atoxyl, Arsacetin, Tryparsamide, Filix-Mas, Methyl Alcohol and Tobacco; the last causes a central scotoma, the others usually contract the field from without inwards. Santonin causes yellow vision. Taste is excited by bitters, aromatics, etc., and paralysed by Cocaine which also abolishes the sense of smell.

2. MOTION.—The motor side of the nervous system can be influenced both directly and also reflexly through sensory neurons.

(*a*) **Motor stimulants** may act on various parts of the motor path from the cerebrum to the muscles. Alcohol, general anæsthetics, and Cannabis Indica, by depressing first the higher inhibitory and perceptive centres, may increase the activity of the *motor area.* Direct stimulation of the motor area is a characteristic of the action of Caffeine, Atropine, and Cocaine. The *medullary centres,* especially the respiratory, are stimulated directly by Picrotoxin, Nikethamide, Leptazol, Strychnine, Caffeine, and Atropine and reflexly by local sensory stimulants; the vagus centre is stimulated by the glycosides of Digitalis and Strophanthus, while Apomorphine excites the vomiting centre. The *reflex activity* of the spinal cord is powerfully stimulated by Strychnine, and to a slight extent by Morphine, Codeine, and Caffeine.

At the *myoneural terminations* of the *voluntary nerves,* Acetylcholine is formed and acts as the excitor of the muscle receptors; Acetylcholine is rapidly hydrolysed by cholinesterase, but Physostigmine and Neostigmine inhibit the action of cholinesterase and thus intensify or prolong the action of Acetylcholine on the voluntary muscle receptors; Tetra-ethyl Pyrophosphate and Di-*iso*propyl-fluorophosphonate have similar actions. *Parasympathetic endings,* motor or secretory, are also cholinergic, and here also Physostigmine and Neostigmine prolong the effect of the secreted Acetylcholine and so produce the effects of parasympathetic stimulation. Acetyl-β-methylcholine, Carbachol, Pilocarpine, Muscarine and Arecoline act directly on the parasympathetic muscle receptors like Acetylcholine.

At *sympathetic endings,* Adrenaline is the natural hormone, which is rapidly oxidized by amine-oxydase. Ephedrine and Amphetamine inhibit amine-oxydase and so potentiate and prolong the action of Adrenaline. The sympathetic endings supplying the sweat glands are cholinergic. Ergotoxine stimulates but in large doses paralyses motor, but not inhibitory, sympathetic endings.

The *muscles* themselves may be stimulated by the faradic and galvanic currents, by massage, passive movements and exercise. Barium, Veratrine, and Calcium alter the form of the muscle curve. *Involuntary muscle tissue* is stimulated directly by Pituitrin, Digitalis and Histamine.

(*b*) **Motor depressants.**—The *motor convolutions* are directly depressed by Hyoscine, Bromides, Phenobarbitone, Methylphenobarbitone (Phemitone) and Phenytoin Sodium; and completely paralysed by general anæsthetics, which arrest all voluntary and reflex movements. The *medullary centre of respiration* is powerfully depressed by Opium, Diamorphine, Codeine, Hyoscine, Hydrocyanic Acid, and toxic amounts of Alcohol, Chloroform, Ether and organic hypnotics; death from over-dosage with these drugs occurs from respiratory failure. *Motor and secretory ganglia,* although stimulated by small doses, are paralysed by large doses of Nicotine, Lobeline, and Coniine. The *voluntary motor nerve endings* are depressed and paralysed by Tubocurarine, which antagonizes Acetylcholine formed at voluntary motor endings and in ganglia. Flaxedil and Decamethonium Iodide act similarly. *Parasympathetic motor* and *secretory endings* are paralysed by Atropine, Hyoscyamine, and Hyoscine, which antagonize Acetylcholine formed at parasympathetic endings. *Inhibitory sympathetic nerve endings* to involuntary muscle are stimulated by Adrenaline, and *involuntary muscle* is directly relaxed by Nitrites, Benzyl Benzoate, and Chloroform.

(*c*) The **co-ordination of movements,** regulated mainly by the cerebellum, is interfered with by Alcohol.

3. CONSCIOUSNESS.—The highest cerebral centres can be subjected to a variety of influences.

(*a*) *Consciousness can be stimulated* or aroused by sensory, especially painful, stimuli: for instance, the cold bath; irritant applications, such as Mustard, to the skin; loud sounds; or irritant smells. Caffeine, and to a lesser extent Cocaine, directly stimulate the intellect and higher cerebral centres, and relieve fatigue probably by accelerating oxidation processes.

The mental faculties are readily *disordered* by Alcohol, which depresses first the highest faculties of criticism, anxiety, fear and shyness, causes an apparent stimulation of intellect and a feeling of brilliancy, followed by confusion of thought and judgment, emotional disturbance and loss of inhibitory or will-power. Opium, Cannabis Indica, and to a lesser extent the organic hypnotics, which first depress the perceptive and sensory areas, may cause brilliancy of imagination, fantastic ideas or dreams associated with diminished sense of time and space from the elimination of external impressions.

(*b*) *Consciousness can be reduced* or abolished and thus **general anæsthesia** produced by means of drugs that *directly depress the nervous tissue of the convolutions* by a physico-chemical action on the lipoid constituents of the cells. Such are Chloroform, Ether, Ethyl Chloride, Nitrous Oxide, and large doses of organic hypnotics (basal anæsthetics), e.g. Paraldehyde, Bromethol, Thiopentone and Hexobarbitone Sodium. The advantage of general anæsthetics lies in the fact that they produce complete depression of the cerebral centres before seriously impairing the functions of the vital centres in the medulla. Opium and the alkaloids Morphine, Codeine, and Diamorphine relieve pain by depressing the sensory cortex but very readily depress also the respiratory centre; this, and the fact that they augment spinal reflexes, precludes their use as general anæsthetics. Hyoscine, which impairs memory and depresses the motor area, also depresses the respiratory centre, and although a combination of Morphine and Hyoscine has been used (twilight sleep) to allay pain and restlessness in child-birth, there is a risk to the respiratory centres of both mother and child.

In selecting drugs to diminish consciousness, the general anæsthetics are chosen for operative procedures when complete abolition of sensation and reflex action is essential; the depressants of the sensory area (anodyne narcotics) are used when continuous pain must be relieved so as to permit sleep; and the depressants of the perceptive centres—the organic hypnotics or Bromides—when pain is absent and all that is necessary to cause sleep is the elimination of external impressions.

4. SLEEP.—To secure sleep it is essential to eliminate all afferent impressions: thus we may be able to secure mental calm by the absence of noise, light and other external impressions, and by relief of pain or such disturbing sensations as attend indigestion, heart disease and cough. Along with these *indirect hypnotic* measures we may employ **direct hypnotics** which depress the perceptive, but not the sensory (pain), centres of the cerebrum. Artificial sleep is readily induced by such hypnotics as Paraldehyde, Chloral Hydrate, Chloral Formamide, Sulphonal, Barbitone, Phenobarbitone, Butobarbitone, Pentobarbitone, Cyclobarbitone and Hexobarbitone. It is important to know the time each takes to induce sleep, the duration of the effect and the state of the patient on waking (p. 303 *et seq.*). For patients who have difficulty in going to sleep a short-acting hypnotic may suffice whereas for the easily awakened patient a long-acting hypnotic is desirable. Bromides and Hyoscine, which depress the motor cortex, are of special value when sleeplessness is due to restlessness or delirium.

THERAPEUTICS

The therapeutics of the nervous system can best be considered by reference to its chief disorders.

1. **Disturbances of sensation: pain, and the use of anodynes.** It is

important to ascertain the pathological cause of pain or sensory discomfort before employing sedatives to relieve it. Pain of an abscess is relieved by incision, of acute rheumatism with Salicylates, of fibrositis with massage, of colic with a purgative. These are *indirect anodynes,* because they remove the pathological cause of the pain, without acting upon nervous tissue. *For practical purposes,* anodynes may be classified into (1) *indirect anodynes;* (2) *local anodynes or local anæsthetics which act on the peripheral nerves only;* (3) *anodyne antipyretics which act on the thalamic pain centres;* and (4) *anodyne narcotics which depress the sensory area of the cerebral cortex.*

(*a*) *Indirect anodynes* include rest and surgical operations; simple physical protectives, such as ointments in skin diseases and the local use of poultices and warm fomentations, and cold applications.

(*b*) *Local anodynes.*—Local sensory irritants, e.g. Ammonia, Turpentine, Camphor, Menthol, Methyl Salicylate, etc., produce, after a primary irritation, a depression of sensory nerve endings and are therefore used to relieve mild degrees of superficial—especially referred—pain, e.g. of neuralgia, fibrositis, myalgia and lumbago, in the form of liniments such as Linimentum Camphoræ Ammoniatum or Linimentum Terebinthinæ. Atropine and Aconitine are also mild local anodynes; hence Linimentum Belladonnæ or Aconiti are used for similar purposes. Phenol and Clove Oil are used as anodynes (obtundents) to relieve pain in sensitive dentine.

(*c*) *Local anæsthetics.*—When a more powerful local anodyne action, which will permit of painless incision, is desired, local anæsthetics must be chosen. If only a superficial incision is required, the part may be frozen by a spray of Ethyl Chloride or for mucous membranes, e.g. conjunctival, nasal, buccal, urethral, 1 to 5 per cent. solutions of Cocaine Hydrochloride or other absorbable *surface anæsthetic* is used. Procaine, Cinchocaine, Butacaine, Amethocaine or Xylocaine may be injected hypodermically, infiltrated in dilute solution around the area, or injected around an accessible part of the nerve trunk supplying the part (regional anæsthesia or nerve-blocking). The addition of Adrenaline to local anæsthetic solutions reduces hæmorrhage and confines, as well as prolongs, the local action of the anæsthetic by retarding its general absorption. It should be noted that local anæsthetics may fail to anæsthetize inflamed tissues, and their injection into these causes great pain. Intraspinal anæsthesia for operative purposes is effected by means of Procaine, Cinchocaine or Amethocaine.

(*d*) *Anodyne antipyretics.*—These are of considerable value in relieving moderate pain, such as that of neuralgia, headache, myalgia, or pain arising from wounds, teeth, or fibrositis, particularly because anodyne antipyretics do not interfere with the intellectual functions. Acetylsalicylic Acid, Phenacetin, or Phenazone often suffice to render such painful impressions tolerable and thus permit sleep. Migraine is relieved by a hypodermic injection of Ergotamine Tartrate, but its peripheral vasoconstrictor action must be watched; Urea, given orally, is often effective in migraine.

(*e*) *Anodyne narcotics and general anæsthetics.*—When pain renders sleep impossible, and the patient is distressed, anodyne narcotics are demanded. Opium or Morphine is most useful for severe and persistent pain, especially that of abdominal disease, renal and biliary colic, of carcinoma and after operations; hypodermic injection of Morphine Hydrochloride is most satisfactory in urgent cases. Codeine and Diamorphine are less effective in relieving pain but less liable to cause nausea or constipation; the latter, like Morphine, is habit-forming. Papaveretum (Omnopon) is regarded as having less side-effects than Morphine. Papaverine and Pethidine relax spasm but are less powerful anodynes. Disephonine and Heptalgin are also useful substitutes for Morphine.

If pain is unbearable, *general anæsthetics* must be employed. Such are the pains of labour, or the pain attending the reduction of a dislocation or setting of fractures.

2. **Paralysis.**—Loss of motor power is a frequent symptom of disease of the nervous system and is of several different types. Its treatment necessarily varies according to which centres or tracts have been involved in the pathological process. Whatever be the nature of the paralysis, care must be taken by splinting or other means that the paralysed muscles are guarded from stretching and the healthy antagonist muscles prevented from producing contractures. The rigidity of lesions of the extra-pyramidal system such as *paralysis agitans* and *chronic encephalitis lethargica* is considerably relieved by Hyoscine Hydrobromide.

Paralysis of the *upper motor neuron*, as in hemiplegia or disseminated sclerosis, is treated by exercises and massage. Strychnine is contra-indicated because reflex activity is often already increased from lack of pyramidal control. Reflex spasms are relieved by Bromides and the urgency of micturition, which is the earliest sphincter disorder in this type of nervous disease, responds to Atropine.

Paralysis of the *lower motor neuron*, when due to progressive muscular atrophy, is sometimes benefited by Strychnine. *Infantile paralysis* is best treated for the first few weeks by absolute rest of the affected muscles, and later by carefully graduated movements. *Peripheral neuritis* is treated by careful splinting, while the nutrition of the paralysed muscles is maintained with the help of massage and electrical treatment; administration of Vitamin B_1 (Aneurine Hydrochloride) hastens recovery in the alcoholic form.

The motor disabilities of diseases of the *posterior columns*, e.g. tabes dorsalis, are due to interference with afferent impulses from muscles and joints and are treated by re-education exercises. The delayed micturition and overflow incontinence of tabes may be benefited by Strychnine. *Hysterical paralysis* is treated by psychotherapy, and mixtures containing Tinctura Valerianæ Ammoniata are occasionally of service.

Myasthenia gravis, due to deficiency of Acetylcholine at the voluntary motor endings, is treated by Neostigmine which has less parasympathetic effects than Physostigmine and has a longer action; the parasympathetic actions may be annulled by Atropine. Ephedrine potentiates the effect of Neostigmine. Tetraethyl-pyrophosphate and Di-*iso*propyl-fluorophosphonate have also been used in myasthenia gravis. Quinine Hydrochloride, 0·6 G (10 gr.) daily, relieves myotonia congenita and Potassium Chloride, 10 G daily, improves familial periodic paralysis.

3. **Increased intracranial tension,** when arising acutely as in apoplexy, meningitis or uræmia, is best treated by lumbar puncture and the withdrawal of cerebro-spinal fluid. This operation must be performed only after due consideration, because in the presence of a cerebral tumour or œdema of the brain, foraminal crowding may be induced. In chronic cases, due to cerebral tumour, the tension may be lowered and headache relieved by promoting dehydration of the brain. This may be accomplished (1) by giving hypertonic saline or hydragogue purgatives whereby fluid is drained from the circulation into the bowel; or (2) by an intravenous injection of 50 Mils of a 50 per cent. Glucose or Sucrose solution daily so that the osmotic tension of the blood is increased and fluid thus abstracted from the brain.

4. **Excessive motor activity** in the form of *convulsions*, especially

in children, is often due to an infection such as broncho-pneumonia, or an acute specific fever, or hypocalcæmia, or to peripheral irritation from worms; these are treated by attention to the cause. Repeated convulsions are treated by immersing the child in a hot mustard-bath and by administering Bromides and Chloral Hydrate or Paraldehyde per rectum after a preliminary enema. In *epilepsy*, Phenobarbitone, Methylphenobarbitone, Phenytoin Sodium, Tridione and Bromides serve in reducing the frequency and severity of the fits; Bromides cause acne and more mental depression. In *delirium tremens*, mania and other conditions characterized by marked mental excitement, an injection of Hyoscine and Morphine produces rapid amelioration of the symptoms. *Chorea* frequently subsides by complete rest, but Acetylsalicylic Acid assists recovery and Chlorbutol or Phenobarbitone will reduce the movements. Tetanus and hydrophobia require treatment by the appropriate antitoxin.

Meningococcal meningitis is a septicæmia; lumbar drainage is performed and full intravenous doses of Sodium Sulphathiazole or Sulphadiazine given and followed by oral dosage. Penicillin may be injected intramuscularly and also intrathecally, 15,000 Units once or twice daily, as it does not penetrate into the cerebrospinal fluid. Tuberculous meningitis requires prolonged dosage with Streptomycin.

5. **Loss of consciousness,** in cases of fainting, drowning, injuries to the head, etc., requires treatment by stimulants to the respiratory centre, such as an injection of Strychnine, Caffeine and Sodium Benzoate, Nikethamide or Leptazol, and rapidly acting circulatory stimulants, such as Adrenaline or Methylamphetamine. Local sensory stimulants, such as cold affusion, brandy or whisky by mouth, or inhalation of Ammonia, are reflex circulatory and respiratory stimulants in emergency. Narcolepsy is treated during the day by Amphetamine Sulphate.

6. **Sleeplessness** will be rationally treated by selecting an appropriate hypnotic, after full trial has been made of the indirect means of promoting sleep (p. 556). *Insomnia,* if it is due to mental worry or excitement, may be overcome by short or intermediate-acting hypnotics, e.g. Paraldehyde, Chlorbutol, Carbromal, Allobarbitone, Butobarbitone, Cyclobarbitone or Hexobarbitone. For patients who awake easily, the longer-acting hypnotics, e.g. Chloral Hydrate and Barbitone, are more suitable. Sulphonal is rarely used except for mental cases. Bromides are indicated when there is restlessness, mental distress or intellectual

overwork but they are not rapid or reliable hypnotics. Paraldehyde and Carbromal are particularly useful in insomnia associated with respiratory or cardiac distress. If pain prevents sleep, a hypodermic injection of Morphine or other anodyne narcotic is given. Small amounts of Alcohol at bedtime often induce sleep by relieving anxiety and worry. In every instance the time for administration of hypnotics must be carefully ordered. Further, it must never be forgotten that the narcotics, including Opium, Barbitone, and Chloral Hydrate, may create a deplorable drug-habit, and may depress the respiratory centre.

CHAPTER XI

THE KIDNEYS

PHARMACOLOGY

THE blood-pressure in the glomerulus causes the filtration of water and of all the non-colloidal constituents of the plasma, e.g. urea, uric acid, salts, glucose and amino-acids, through the thin walls of the glomerular capillaries, but no filtration of the blood colloids occurs. The fluid filtered into the Bowman's capsule passes downwards to the convoluted tubules, where the epithelium possesses the power of reabsorbing from the glomerular filtrate a fluid of the same crystalloid composition as normal blood plasma; thus, valuable salts, glucose, amino-acids and uric acid return to a certain extent (*threshold*) to the blood, while excretory materials, e.g. urea, abnormal salts, creatinin, alkaloids, etc., are not reabsorbed (*no threshold*); also if the blood be hydræmic, any excess of water filtered out will not be reabsorbed. But the cells of the convoluted tubules can form hippuric acid and ammonia; the latter is returned to the blood if required to adjust its reaction, but is usually excreted; the tubules excrete urea, uric acid, sulphates and phosphates, so that the concentration of these excretory materials in the glomerular filtrate is increased as it passes through the tubules. The acidity of the urine is maintained because the tubules reabsorb the essential basic ions, but leave the acid radicles in the urine. The presence of urea which is not reabsorbed by the tubules will, by increasing the osmotic pressure in them, reduce the reabsorption of fluid.

The rate of glomerular filtration depends on the difference of pressure between the blood and the interior of Bowman's capsule *minus* the osmotic pressure of the proteins in the plasma. The size of the vessels and, therefore, the glomerular blood-pressure is regulated by vaso-constrictor and vaso-dilator nerves from the renal plexuses.

Influence of digestion on the urine.—During gastric digestion some H-ions are withdrawn from the blood to furnish the gastric juice, and this loss is shown in the urine, which soon becomes less acid, or even alkaline. When absorption of food begins, water and alkaline salts enter the blood, and augment still further the alkalinity of the urine; but three or four hours after a meal, the urine is again acid.

Renal permeability.—There is a normal *renal leak-point* or *threshold* for the blood constituents; thus, if the percentage of salts in the blood exceeds the normal, e.g. for chlorides 0·5 per cent., the excess is excreted. The normal renal leak-point for blood-glucose is 0·18 per cent.; for blood-urea, 0·02 to 0·04 per cent.; for uric acid, 0·003 per cent. The leak-point or threshold may fall or rise; thus a lowering of the glucose leak-point leads to renal glycosuria, and a rise in the respective leak-points results in retention of chlorides or nitrogen in nephritis, or to uric-acid retention in gout.

The preceding facts show that the functions of the kidney can be modified mainly through the circulation and blood.

1. **Measures for increasing the volume of urine.**—The amount of water filtered through the glomerulus may be increased by **diuretics**, which act in several ways.

(*a*) *By increasing the blood-flow through the renal vessels.*—This is effected by raising the force or frequency of the heart, by improving the blood-flow through the kidneys, or by dilating the renal arteries. Drugs acting in these ways are called **cardiovascular diuretics**, and to this group belong Digitalis, Strophanthus, Squill, Caffeine, Theobromine and Theophylline, which, by their action on the heart, accelerate the flow of blood through the kidneys, bring more glomeruli into active use and thus increase filtration. Active dilatation of the renal arteries is stated to occur in the early stages of the action of Digitalis, Strophanthus, Squill, and Caffeine, but more probably the increased volume of the kidney is a secondary effect of the improved circulation.

(*b*) *By increasing the volume and hydræmia of the blood and lowering its protein osmotic tension.*—This results from drinking fluids; from injecting Normal Saline Solution intravenously, subcutaneously and per rectum; or from administering by mouth absorbable salines, e.g. Potassium Acetate, Citrate, Acid Tartrate or Nitrate, which have a low renal threshold. **Saline diuretics** raise the osmotic tension of the plasma, and fluid is drawn from the tissues into the blood to adjust the balance, the blood is rendered more hydræmic (lowered colloid content) and increased filtration of water results.

(*c*) *By reducing reabsorption from the tubules—no-threshold* *substances.*—In the tubules, water and crystalloids are to some extent (*the threshold*) reabsorbed. Others (*no-threshold substances*) are not reabsorbed, and in the tubules these, by raising osmotic tension,. prevent the normal reabsorption of water. This forms part of the diuretic action of the saline diuretics, and is the chief action of Urea and of Ammonium Acetate and Citrate which are excreted as Urea. Mersalyl and other mercurials, e.g. Calomel, also act by decreasing tubular reabsorption of water. The Injection of Mersalyl contains Theophylline which prevents its ionization into irritant mercuric compounds in the kidney.

(*d*) *By irritating the renal epithelium during excretion.*—This is the cause of the diuretic action of the Volatile Oils, such as Copaiba, Cubebs, Juniper, and Sandalwood Oil; they are obsolete diuretics.

2. **Measures for diminishing the volume of urine.**—The volume of urine is diminished by saline and hydragogue purgatives, which drain fluid from the body, and by excessive dosage of Digitalis, which produces constriction of the renal arteries. Warmth of the body lessens urinary secretion by promoting diaphoresis. Posterior Pituitary Extract (vaso-pressin) produces an antidiuretic effect which reaches a maximum in about three hours and passes off in ten hours; it increases the reabsorption of water by the tubules.

3. **Measures influencing the composition of the urine.**—Alterations in the composition of the blood resulting from the composition and quantity of food and the activity of hepatic and tissue metabolism, as modified by exercise, etc., produce variations in the composition and relative proportions of the urinary solids.

(*a*) The *natural acidity of the urine can be increased* slightly by giving Acid Sodium Phosphate, but to a greater degree by Ammonium Chloride or Nitrate and Calcium Chloride; Salicylic and Benzoic Acids also raise the urinary acidity. The mineral acids do not materially increase the acidity of the urine because they are excreted mainly as neutral salts of ammonia, which is formed by the renal tubules to protect the alkali reserve of the blood.

(*b*) *The urine may be rendered alkaline* by administering Sodium Bicarbonate, but this will disturb digestion by neutralizing the gastric acid. Citrates, Tartrates and Acetates of Sodium or Potassium have no action in the stomach but are oxidized in the tissues and excreted as bicarbonates in the urine, hence they are more suitable as *remote antacids.*

(*c*) The *excretion of uric acid* is greatly increased by Cinchophen, which lowers the renal threshold for uric acid, and thus reduces the amount in the blood.

4. **The bladder and urinary passages.**—The parasympathetic motor nerve endings in the ureter and bladder are depressed by Atropine, Hyoscyamine and Hyoscine, which act as sedatives to the urinary tract, and relieve reflex spasm from ureteral calculus. Carbachol is useful to overcome post-operative urinary retention. As the sympathetic innervation constricts the sphincter muscle but relaxes the tone of the detrusor muscle of the bladder, Ephedrine is a valuable means of controlling incontinence of urine.

We may exert an *antiseptic action* on the urinary passages by (1) Penicillin, which during its excretion by the kidney is effective against gonococci, streptococci, staphylococci, but not against E. coli or B. proteus: (2) Sulphonamides, particularly Sulphanilamide, Sulphacetamide, Sulphadimidine and Sulphamerazine, from which crystalluria is unlikely. A loading dose is unnecessary as the drug becomes concentrated in the urine. They are effective for gonococci, streptococci, staphylococci, and usually for E. coli and B. proteus; (3) Ammonium or Calcium Mandelate, which are excreted as mandelic acid, is often successful in resistant E. coli infections if the urinary reaction is kept at or below *p*H 5·6; (4) A highly acid urine, produced by Ammonium Chloride or Calcium Chloride, tends to inhibit E. coli; (5) An alkaline urine, formed by Potassium or Sodium Citrate, also impairs urinary bacterial growth; (6) Hexamine, converted in acid urine to Formaldehyde, is obsolete as Penicillin and Sulphonamides are superior; (7) The Volatile Oils are also obsolete as urinary antiseptics.

THERAPEUTICS

The rational treatment of renal or urinary disorders must be founded upon an appreciation of the influences of other organs on the kidneys.

1. **Renal congestion from disease of the heart.**—This may be taken as the type of renal disorder from defective circulation, and the rational treatment is obvious, namely the restoration of a normal circulation by strengthening the heart. The *cardio-vascular diuretics*, Digitalis, Strophanthus and Squill, fulfil this requirement; Theophylline and Ethylenediamine, Theophylline and Sodium Acetate, Theobromine and Sodium Salicylate or Caffeine may be used as adjuvants by increasing renal filtration. Saline diuretics, e.g. Potassium Acetate and Citrate, also assist in removing œdematous fluid by increasing the filtration of water

from the glomerulus and preventing its reabsorption by the tubules. Injection of Mersalyl is the most powerful diuretic for the removal of œdema of cardiac origin.

2. **Acute nephritis.**—The excretion by the kidneys of an irritant, e.g. a Volatile Oil or a heavy metal, is occasionally the cause of this disease; more commonly it is due to the effects of a streptococcal infection. It frequently follows an attack of acute tonsillitis or scarlet fever, and in the latter disease its incidence as a complication has been reduced by the routine administration of alkalis. The attack of acute nephritis is commonly ushered in by oliguria or suppression, and in order to rest the kidneys as far as possible the intake of fluid and Sodium Chloride should be reduced to the minimum and food withheld for the first two or three days. The patient is confined to bed and must be kept warm and shielded from draughts. If septic foci still exist, Penicillin may be injected. From the third day, a pint and a half of fluid may be given mainly in the form of orange juice which may later be gradually substituted by milk. Bread and butter, biscuits, jam and farinas are added and limited protein is subsequently permitted, if improvement is maintained.

Drugs, including diuretics, are generally contra-indicated in acute nephritis, as the kidneys are temporarily incapable of functioning.

If anuria results from renal surgical operations, an intravenous drip of 4·3 per cent. Sodium Sulphate in amount of 500 Mils may restore the renal function. If symptoms of increased intracranial pressure arise (hypertensive encephalopathy) lumbar puncture should be performed and 100 Mils of hypertonic (50 per cent.) Dextrose injected intravenously to dehydrate the brain.

3. **Chronic nephritis with œdema and salt retention** is a sequel of acute nephritis or may arise insidiously. Œdema with retention of sodium is the prominent symptom; the nitrogen excretion, in a typical case, is normal. The œdema may be reduced by ordering a salt-free diet. Urea is a valuable diuretic and a diet with a high protein content is efficacious in diminishing œdema because of the katabolism of protein to form urea. Saline diuretics should be avoided as they are liable to increase the œdema. Injection of Mersalyl intramuscularly, in small doses at first, is frequently effective in reducing the œdema; if it is well tolerated, Ammonium Chloride may be given to enhance its action.

4. **Chronic nephritis with nitrogen retention.**—This form of nephritis, associated with sclerosis of the kidney, may arise

insidiously or be a sequel to acute nephritis when water and salt retention simultaneously with nitrogen retention are frequently seen. In the early stages of nephrosclerosis, the progress of which may have been hastened by over-indulgence in food and alcohol, treatment consists in thorough reform of diet, free purgation and elimination generally. Salt and fluids are permitted, and Potassium Citrate as an antacid diuretic is often beneficial. In the more advanced and graver form with high arterial tension, the disease is usually beyond our control, and treatment has to be directed towards removing its sequelæ and relieving distress. The food should be moderate in quantity, and chiefly non-nitrogenous; stimulants must be avoided; carbohydrates and fruits may be taken freely; moderate rest of body and mind is ensured; the skin kept active, short of provoking chill, and—if practicable—by residence in a mild climate. Uræmic twitching is often associated with hypocalcæmia and can be relieved temporarily by Injection of Calcium Gluconate (20 Mils) intramuscularly or intravenously. Uræmic symptoms may be mitigated by lumbar puncture.

5. **Diabetes insipidus.**—The polyuria of diabetes insipidus can be controlled for a day by injections of Posterior Pituitary Extract (Vasopressin); one daily injection may suffice, if it is supplemented by intra-nasal administration by soaking a pledget of cotton-wool with the extract, or an injection of Vasopressin Tannate suspended in oil has a longer action.

6. **Renal disorders of permeability.**—When the renal leak-point or threshold is modified by disease, treatment involves rational modification of the diet; and in some cases drugs are useful. In *renal glycosuria* the threshold may be lowered to near the normal blood-sugar level (0·1 per cent.); in such a case glycosuria will occur even if carbohydrate be restricted, and the blood-sugar will always be below normal (hypoglycæmia). The condition is not serious and treatment is unnecessary. In *uric-acid diathesis and gout* the uric acid of the blood may rise to 0·006 per cent., while that excreted in the urine is deficient. The purin content of the diet must be limited, and the renal permeability for uric acid increased, if necessary, by giving Cinchophen, which lowers the threshold effectively and removes the uric acid, but it should be given intermittently in four-day periods and a watch kept for signs of toxic effects on the liver. Posterior Pituitary Extract lowers the threshold for chlorides, and Phloridzin lowers the glucose threshold.

7. **Renal disorders of alimentary origin.**—Phosphaturia is

rationally treated by dietetic modification and drugs, e.g. Ammonium Chloride or Acid Sodium Phosphate, to render the urine acid. High acidity of urine is treated by restriction of proteins and by giving Sodium Citrate or Tartrate.

When uric-acid gravel or calculus is present, diuretics, especially Potassium Citrate, are used, and abundant water-drinking.

8. **Urinary antiseptics.**—The renal pelvis and the bladder are frequently the seat of catarrhal inflammation due to invasion by the Escherichia coli or the pyogenic cocci. The E. coli flourishes best in a slightly acid urine, and if the urine is made strongly alkaline by giving large doses of Sodium Bicarbonate or Potassium Citrate this is often sufficient to bring about a cure in mild infections. The growth of E. coli is also restricted by a highly acid urine and this can be achieved by the administration of Ammonium Chloride or Nitrate until the reaction of the urine is maintained at or below *p*H 5·6 (neutral red being used as indicator). At this high acidity, Mandelic Acid has a powerful bactericidal action on E. coli and its excretion in the urine is maintained by oral dosage with Ammonium or Calcium Mandelate in 3 G (45 gr.) doses four times daily. Ammonium Mandelate is best because, owing to the conversion of the Ammonium ion to urea, there is liberated Mandelic acid which itself raises the urinary acidity and thus smaller doses of Ammonium Chloride will keep up the requisite degree of acidity.

Sulphanilamide, Sulphacetamide, Sulphadiazine or Sulphadimidine is usually effective for E. coli, B. proteus, staphylococcal and streptococcal infections, but less useful than Mandelic Acid for S. fæcalis. Streptomycin will eliminate many Gram-negative organisms, such as B. proteus, which are resistant to other urinary antiseptics. Gonorrhœal infections are successfully treated by Penicillin within a day but it may mask a simultaneous syphilitic infection.

9. **Spasm of the ureteral and vesical musculature.**—The agonizing pain of ureteral colic which occurs during the transmission of a calculus from the renal pelvis is alleviated by a full dose of Atropine Sulphate 1 mg. (1/60 gr.) and Morphine Hydrochloride 15 mg (1/4 gr.) given simultaneously, or by Pethidine or Papaverine which relax the muscle as well as relieve the pain. Atropine is also of value where there is defective voluntary control of the vesical sphincter, as occurs in diseases of the pyramidal tract and in enuresis. Sympathetic stimulants, particularly Ephedrine, are useful in incontinence of urine from loss of tone in the sphincter.

CHAPTER XII

THE BODY-HEAT, AND ITS REGULATION: THE SKIN

PHARMACOLOGY

THE heat-regulating or thermogenetic centre in the hypothalamus maintains the normal body-temperature at about 98·4° F. (36·9° C.). The centre receives from the afferent thermal nerves in the skin and mucous membranes impressions of temperature which are transmitted to the cerebrum, as sensations of temperature; to the sweat-centres in the cord; to the metabolic centres; and to the vaso-motor, cardiac and respiratory centres.

When the surrounding temperature rises, (1) there is increased loss of heat by dilatation of cutaneous vessels, by perspiration, and by accelerated respiration, and (2) there is diminished production of heat, resulting from inactivity of the muscles. Increased metabolic activity due to exercise produces dilatation of the skin vessels and accelerated respiration in order to get rid of the extra heat produced.

If the surrounding temperature be lowered, the heat-regulating centre causes (1) diminished loss of heat, by contracting the cutaneous vessels, arresting perspiration, and slowing respiration; and (2) increased production of heat by inducing increased metabolism in the muscles: shivering and rigors are reflex efforts to increase heat-production at the onset of febrile illness.

The sweat-glands are excretory glands for water, salts, and to a slight extent for nitrogenous products. They are controlled by nervous influences through sympathetic (but *cholinergic*) nerves with centres in the spinal cord.

1. **External temperature.**—The air of a room or ward can be cooled or warmed to suit particular diseases; in pulmonary disease it should be kept between 60° and 65° F. A change to a milder, or sub-tropical climate, such as that of Madeira, Egypt or the Riviera, may be recommended for patients liable to bronchial inflammation during the winter. When a rapid modification of the cutaneous temperature is desired, baths, wet-packs and sponging are used (*see* p. 582). A cool bath at a temperature

of about 60° F. (15·5° C.) rapidly lowers body-temperature; and the cold wet-pack, cold douche, or sponging a part or the whole of the exposed skin with cold or even tepid water, has a similar effect. These measures are known as **external refrigerants.**

2. **The cutaneous circulation.**—Dilatation of the cutaneous vessels by means of the warm bath, by Alcohol, by Spiritus Ætheris Nitrosi or by hot drinks, is a useful method of increasing heat-loss. Pulvis Ipecacuanhæ et Opii (Dover's Powder) acts mainly in lowering temperature by dilating the cutaneous vessels.

3. **The sweat-glands**: *diaphoretics, sudorifics, anhidrotics.*—(*a*) Measures which increase the amount of perspiration are called **diaphoretics,** and those which cause profuse sweating are termed **sudorifics.** The afferent thermic nerves in the skin can be readily stimulated by means of heat, whether by moist heat in the form of the warm-water or vapour bath, or of packs by dry heat, as in the Turkish and radiant-heat baths; or by general warmth of the air, the room or the clothing. The sweat-centres may be stimulated reflexly through other afferent nerves, such as those of the mouth, throat and stomach, by means of hot spiced drinks, or emetic drugs, such as Antimony and Ipecacuanha. Perspiration may sometimes occur from a direct action on the spinal sweat-centres, as is seen in poisoning by Strychnine and, possibly, Camphor. The centres are also stimulated by venous blood. The sympathetic nerve endings in the sweat-glands are cholinergic and are stimulated by Pilocarpine, Physostigmine, Carbachol, and Muscarine, which cause a profuse and rapid flow of sweat. In hypoglycæmic coma, sweating is a prominent symptom.

Salicylates and other central antipyretics act as diaphoretics by an action on the heat-regulating mechanism which conveys impulses to the sweat-centres.

(*b*) Measures which diminish the amount of perspiration are called **anhidrotics.** Some of these act upon the afferent nerves, especially moderate local cold, obtained by fanning, light clothing and a cool atmosphere generally; and sponging with cool or tepid water. External astringents which diminish secretion by precipitating proteins in the glandular epithelium and harden the skin are also useful in localized sweating; such as metallic and vegetable astringents, Formaldehyde and Alcohol. Night sweats are often due to impaired respiration and are obviated by fresh air and lighter bed-clothing. The efferent secretory nerve terminations are depressed or paralysed by Atropine, Hyoscyamine and Hyoscine, and the anhidrotic effect of these alkaloids and of the drugs containing them is very marked.

4. **Drugs acting on the heat-regulating centre.**—Sodium Salicylate, Acetylsalicylic Acid, Phenazone, Phenacetin, Amidopyrin and Acetanilide reduce febrile temperature by a selective depressant action on the thermogenetic centre in the hypothalamus; the last two are apt to cause agranulocytosis and methæmoglobinæmia respectively. These *central antipyretics*, by a depressant action on the heat-regulating centre, lower the point of thermal equilibrium in fever; and efferent impulses cause the superfluous heat to be removed by dilatation of the vessels of the skin and sweating. The proofs that they act centrally are: (1) they do not lower temperature in health; in fever they (2) lower temperature even if the sweat-glands be paralysed by Atropine, but (3) not if the cervical cord be cut so as to prevent vaso-dilatation; (4) when temperature falls, there is no shivering; and (5) they lower temperature due to puncture of the hypothalamus.

THERAPEUTICS

In febrile illnesses, the temperature of the room should be maintained at about 60° F., bed-clothing should consist of light blankets, and adequate ventilation is arranged, but the patient must be protected from draughts. Diet of a light character is allowed and care taken to ensure regular evacuation of the bowel.

1. **Physical Measures.**—A temporary reduction of pyrexia is readily achieved by sponging the skin with cool or tepid water, or by the use of a cold-pack or cool bath. Such treatment, by increasing heat-loss, produces a rapid but temporary fall in the temperature, is comforting to the patient and often promotes sleep. If cold sponging is repeated every two hours in persistent fever, it frequently produces a gradual fall in the general level of the temperature.

2. **Diaphoretics.**—The remedies chiefly employed in treating symptomatic fevers, e.g. accompanying infections of the nasal mucosa, fauces, bronchi or lungs, are those which increase heat-loss by dilating the superficial vessels; in warm surroundings these encourage heat-loss through perspiration. The mild diaphoretics include: draughts of hot water, Alcohol (as toddy), Liquor Ammonii Acetatis, Spiritus Ætheris Nitrosi, and Pulvis Ipecacuanhæ et Opii (Dover's Powder).

3. **Central Antipyretics.**—The use of these is particularly of value to lower the point of thermal equilibrium and thus to

promote sweating and the comfort of the patient in acute specific fevers, influenza, laryngeal and bronchial catarrhs and pneumonia. Those commonly employed are Sodium Salicylate, Acetylsalicylic Acid, Phenazone and Phenacetin. They have the advantage that by their analgesic action they relieve the headache and muscular pains which frequently accompany the onset of fever.

4. **Specific Antipyretics.**—The value of Quinine, Mepacrine, Proguanil and Pamaquin in the treatment of malaria is due to their specific toxic influence upon the plasmodium. Sodium Salicylate in acute rheumatism is also a specific and rapidly relieves the fever, joint-pains and swellings; as Salicylates are rapidly excreted, it may be necessary to give doses at two-hourly intervals to maintain an effective concentration in the tissues. The absorbable Sulphonamides are successful in the treatment of hæmolytic streptococcal, staphylococcal, pneumococcal and meningococcal infections; and the less absorbable ones, e.g. Succinylsulphathiazole, are effective for bacillary dysentery and other intestinal infections. Penicillin has a wide range of specific toxicity towards organisms; Streptomycin is bactericidal to M. tuberculosis; Chloromycetin and Aureomycin are effective against typhoid and typhus fevers. The specific anti-toxins for diphtheria, gas gangrene, and tetanus should be used in these diseases.

CHAPTER XIII

A. DRUGS ACTING ON THE SKIN

I. Counter-irritants.—The cutaneous tissues, owing to their rich supply of sensory receptors, are used in therapeutics as a medium from which effects, mainly of a reflex type, can be produced upon the central nervous system by means of counter-irritants, baths, and massage, the latter two measures being discussed in the Appendix.

PHARMACOLOGY.—Counter-irritants may be arranged according to the degree of their action.

1. **Rubefacients** cause first a sensation of heat and an increased circulation (redness) in the skin area to which they are applied; later the feeling of heat is replaced by that of numbness owing to the paralysis of the sensory receptors. The following are used as rubefacients: Hot Linseed Poultices, Mustard Poultices, Cataplasma Kaolini, Turpentine Stupes, and Liquor Iodi Mitis; also Linimentum Camphoræ, Camphoræ Ammoniata, or Terebinthinæ.

2. **Vesicants, Epispastics,** or **Blisters** produce a rubefacient effect, followed by the development of a blister, e.g. Emplastrum Cantharidini, or Liquor Iodi Fortis if applied for a time; they are rarely used.

3. **Pustulants** produce blistering and inflammation of the skin, leading to the passage of leucocytes through the capillaries; e.g. Croton Oil and Tartar Emetic; they are never used.

Phenomena of counter-irritation.—When a counter-irritant is applied to the skin, the *first* effect is *rubefacient.* The cutaneous vessels are dilated by an axon reflex from the sensory endings, hence the part becomes red; and the irritation of the sensory nerves causes pain of a hot burning character. Cutaneous anæsthesia follows later owing to fatigue of the irritability of the sensory receptors and superficial pain is thus relieved; rubefacients are, therefore, sometimes used as local anodynes. Reflexly from the initial sensory irritation, the heart is accelerated, the blood-pressure rises, and the breathing becomes more rapid but often shallower. The cerebral nervous centres of perception and consciousness also are stimulated by the painful impression.

In the *second* degree of counter-irritation—*vesication*—the reddened area becomes inflamed: plasma escapes from the capillaries more rapidly than it can be carried away by the lymph channels, and, since it cannot escape through the *stratum corneum*, the epidermis is raised, and a vesicle is formed. If the blistered surface is extensive, the painful impressions may cause reflex weakening and slowing of the heart, slowing of the respiration, and nervous depression.

In the *third* degree of counter-irritation—*pustulation*—diapedesis of leucocytes occurs, and there results, around the openings of the skin glands, a crop of painful pustules.

Theories of the actions of counter-irritation.—These local and reflex general effects of cutaneous irritants do not fully explain their effects in disease. The relief of *local pain* by a rubefacient is due to depression, following initial stimulation, of the sensory receptors in the skin; but the relief of *remote pain* by counter-irritants is probably entirely psychic, the conducting paths and attention of the sensory area being entirely occupied by the new sensation to the exclusion of others.

Counter-irritants are also considered to influence inflammatory processes in underlying parts and in the viscera. The theories with regard to their effects are these:

1. Rubefacients, by dilating the superficial vessels and capillaries, cause any diseased tissues in *immediate vascular connection* with the area to receive an increased blood supply and consequently much greater numbers of phagocytes to combat the inflammatory processes. This effect of counter-irritation is illustrated by the application of poultices for synovitis, parietal pleurisy, boils and abscesses.

2. The irritation of cutaneous nerves modifies the circulation and functions of internal organs also in a reflex way, the sensory impressions being conveyed to the vaso-motor and trophic centres in the cord or medulla. We know that disease in a viscus leads to pain, not in the viscus, but in an area of skin which derives its nerve supply from the same segment of the cord as the viscus; and it would appear that in disease of a viscus the segment of the cord from which its nerve supply emanates is hypersensitive and, owing to this, there originate the referred pains, hyperæsthesias, muscular rigidities and cramps of visceral disease.

It is known that a sensory irritant, applied to the area in which hyperæsthesia or pain is felt, results not only in the relief of the pain but also in improvements in the function or disorder of the related viscus. This may be explained on the theory that the *powerful sensory impression excites the controlling centres of the viscus to assume a more efficient control over its circulatory and trophic neurons,* and promotes conditions leading to repair of its disordered functions. Examples of the beneficial reflex effects of powerful sensory stimuli are common. Thus a sensory stimulus of the taste-buds induces gastric secretion; a cold douche rouses the higher cerebral centres in hysteria, as does also an offensive taste, e.g. Valerian; while flagellation has been the judicial counter-irritant in defects of cerebral responsibility for ages. The actual effect produced on an internal organ by irritation of its *associated cutaneous area* is still obscure; most probably the circulatory change is towards increase of circulation or hyperæmia; but in other cases contraction of vessels has been noted. It must be emphasized that a counter-irritant, in order to have a satisfactory reflex effect on an internal viscus, must be applied upon the area to which pain, hyperæsthesia, etc., are referred, i.e. to the associated cutaneous area.

II. Skin Protectives and Sedatives.—The protectives for the skin in common use for cosmetic purposes are inert insoluble compounds which are used as dusting powders, e.g. Chalk, Magnesium Carbonate or Oxide, Magnesium Silicate (French Chalk or Talc), Bismuth Carbonate, Zinc Oxide and Hydroxide, usually mixed in varying proportions with Boric Acid and Starch. They are also made up with other protections—Glycerin, Liquid Paraffin, etc.—into pastes, or incorporated with the protective emollients—the various ointment bases—which, by forming a fatty layer on the skin, prevent the evaporation of water and thus render the skin softer and more pliable. Vanishing creams have a superficial cleansing action (*see* p. 384).

III. Skin Disinfectants, Parasiticides and Antiseptics.—Bactericidal agents are used to disinfect the skin, after it has been thoroughly cleansed with soap and water, prior to surgical incisions; the following are in common use: Alcohol 70 per cent., Cetrimide, Liquor Iodi Mitis, Liquor Cresolis Saponatus, Liquor Chloroxylenolis, Biniodide of Mercury in Spirit, Proflavine, and Gentian Violet. As general wound antiseptics, Hydrogen Peroxide, Liquor Sodæ Chlorinatæ Chirurgicalis, and Proflavine are commonly employed but many more are available (*see* p. 422). For skin diseases, most antiseptic substances have been tried either as dusting powders for moist (weeping) infections or as creams or ointments in dry infections; those used are Penicillin, Sulphonamides, Mercurous Chloride, Ammoniated Mercury, Iodine, Resorcinol, Betanaphthol, Ichthammol, Pix Liquida, Pix Carbonis Præparata, Dithranol, etc. As parasiticides, Sulphur and Benzyl Benzoate are used as ointments or lotions for scabies, Dicophane in powders for body lice, and Paraffin Oil, Lauryl Thiocyanate or Dicophane for pediculus capitis.

THERAPEUTICS

The chief diseased conditions which may be treated by **counter-irritation** are: (1) Subacute and chronic inflammation of parts in direct vascular connection with the skin, such as the pleuræ and joints; (2) congestion and inflammation of contiguous organs, for example the lungs; (3) pain in deep or distant parts, such as neuralgia, myalgia, and cardiac and renal pain.

Skin Protectives and Sedatives find a wide use as cosmetics and in dermatological practice in the treatment of superficial inflammatory reactions of the skin to irritation by a dry cold atmosphere, excessive solar radiation, bacterial infections, etc.

Skin Parasiticides are used to treat scabies or infections by pediculi, and **Skin Antiseptics** are employed in such various skin diseases as eczema, ringworm, favus, impetigo contagiosa, psoriasis, etc.

B. DRUGS ACTING ON THE EYE

PHARMACOLOGY.—To the delicate conjunctival membrane, only those drugs which have little or no irritant action can be applied as lotions or ointments. Suitable **conjunctival antiseptics** are Boric Acid (4 per cent., Sulphacetamide Sodium (2·5 per cent.), Penicillin Eye Ointment (1,000 Units per G), Yellow Mercuric Oxide Eye Ointment (1 per cent.), Zinc Sulphate (1/4 to 1 per cent.) and, particularly in gonorrhœal ophthalmia, Penicillin or Sulphacetamide Sodium solutions or Silver Nitrate (1/4 to 1 per cent.); Zinc Sulphate and Silver Nitrate act also as astringents and should be used with care if there be corneal ulceration lest an opacity be formed. For irrigation of the eye, Silver Protein is used as it is not irritating and its antiseptic action is due to the slow liberation of Silver in ionic solution. For **local anæsthesia**, Cocaine Hydrochloride Solution (1 to 2 per cent.), the Lamella (1/50 gr.) or Oculentum Cocainæ (0·25 per cent.), or Butacaine is employed. A 2 per cent. solution of Fluorescein, containing 3 per cent. Sodium Bicarbonate, is useful to locate corneal lacerations which it stains green.

The **secretion of the lachrymal gland** is increased by Pilocarpine and diminished by Atropine, by stimulation and paralysis respectively of the secretory nerve endings.

Drugs which dilate the pupil are termed **mydriatics.** They may produce this effect: (*a*) by paralysing the terminations of the motor oculi (third) nerve—Atropine, Homatropine, Lachesine, Hyoscyamine, and Hyoscine; (*b*) by stimulating the endings of the sympathetic nerves—Cocaine, Adrenaline; (*c*) by depression of the oculo-motor centre—General Anæsthetics (fourth stage owing to asphyxia).

Drugs which diminish the size of the pupil are termed **myotics.** The pupil may be contracted: (*a*) by stimulating the terminations of the third nerve—Physostigmine, Neostigmine, Carbachol, Pilocarpine; (*b*) by stimulation of the oculo-motor centre—Opium and Morphine.

The **intraocular pressure** is increased by Atropine, Hyoscyamine and Hyoscine and to a less extent by Lachesine and Homatropine, as their action is brief. The increase in pressure is due to the dilated iris which constricts the cribriform spaces of Fontana and thus retards the escape of lymph from the anterior chamber into the Canal of Schlemm.

Intraocular pressure is decreased by Physostigmine, Neostigmine, Carbachol, Di-*iso*propylfluorophosphonate and Pilocarpine which, by constricting the pupil, widen the spaces of Fontana and facilitate the egress of lymph.

The mechanism of accommodation may be influenced by drugs. Atropine and its allies paralyse the nerve endings in the ciliary muscle, which relaxes, and thus the elastic choroid increases the tension upon the suspensory ligament so as to render the anterior surface of the lens less convex, that is, accommodates the eye for infinity. Physostigmine and Pilocarpine stimulate the ciliary nerve endings, contract the ciliary muscle which, by pulling forward the elastic choroid, relaxes the tension on the suspensory ligament and thus enables the anterior surface of the lens to become more convex; thus the eye is accommodated for near vision.

THERAPEUTICS.—Mydriatics are employed to dilate the pupil for examination of the fundus oculi, and to prevent adhesions of the iris after operations. Myotics are used to contract the pupil after the use of mydriatics, in photophobia, and alternately with mydriatics to break down adhesions of the iris. The drugs which paralyse accommodation are employed to facilitate examination of the fundus, and in testing the refraction of the lens; their antagonists are used mainly to promote rapid return of accommodation. The drugs which lower intraocular tension relieve **glaucoma**, and are antidotes to the artificial glaucoma produced by over-dosage or frequent use of Atropine.

C. DRUGS ACTING ON THE GENERATIVE SYSTEM

The contractions of the parturient uterus are increased by Posterior Pituitary Extract (Oxytocin) and Ergot (Ergometrine and Ergotoxine). The former acts directly on the muscle and produces increased force and frequency of the rhythmic contractions with intermediate periods of relaxation; with caution, it may be used for uterine inertia in the second stage of labour and is given after labour to avert post-partum hæmorrhage. Ergometrine also acts on the muscle directly and more rapidly than Ergotoxine in stimulating uterine tone and contractions; Ergotoxine, which stimulates motor sympathetic receptors, may, if used frequently, cause peripheral vaso-constriction and eventually gangrene. Ergot preparations are not given during labour as the powerful tone they induce may, by compression, cause fœtal asphyxia, or even uterine rupture. Ergometrine, by its rapid powerful action, is invaluable in post-partum hæmorrhage. Quinine Hydrochloride has the power of exciting uterine contractions at full term and is used with safety to induce labour. Lead salts are ecbolics, as are also large doses of Volatile Oils, e.g. Pennyroyal, Rue, and drastic purgatives; these have been used by unscrupulous persons as **abortifacients.**

Emmenagogues are drugs which restore or increase menstruation. The influence of the Anterior Pituitary and Sex Hormones on the uterine and generative functions is described on pp. 219 to 227.

Aphrodisiacs are drugs which stimulate the sexual instinct. Amongst these are Alcohol, Cannabis Indica, Camphor (at first), which act probably by impairing cerebral inhibition, and Cantharidin (by vesical irritation). Yohimbine (Quebrachine) Hydrochloride (*Dose*—Metric, 3 to 8 mg; Imperial 1/20 to 1/8 gr.) is an aphrodisiac by dilating the genital vessels. Strychnine, by improving reflexes, may act in some cases.

Anaphrodisiacs depress the sexual reflexes. Such are Phenobarbitone, Bromides, Opium, and organic hypnotics.

The uses of the male sex hormones have been described on p. 227).

APPENDIX

DRESSINGS AND THEIR MEDICATION

Cotton-Wool.—Gossypium absorbens. Bleached and absorbent Cotton-Wool is used largely for its protective and absorbent properties as an external surgical dressing to absorb discharges, prevent ingress of germs and protect the wound. It is obtainable medicated with Boric Acid 3 to 7%—*Boric Wool*; Ferric Chloride 15%—*Styptic Wool.* Being a non-conductor of heat, Cotton-Wool is applied to conserve heat on the chest and back in respiratory complaints, or on inflamed or rheumatic joints; in these cases it may be medicated with Turpentine, with oleo-resin of Capsicum 5% and Methyl Salicylate 1%—*Capsicum or Thermogene Wool.* Unbleached or non-absorbent Wool is employed for padding splints.

Cellulose Wadding (Tillman's Dressing) consists of very fine layers of wood fibre. It is not quite so absorbent nor so elastic as Cotton-Wool, but is cheaper. Hartmann's Wood Wool or Wadding is made from pine wood impregnated with Mercuric Chloride. Cellulose Tissue is Cellulose Wool enclosed in absorbent gauze.

Gauze, Bleached or Plain.—Carbasus absorbens. A loose-woven muslin (6 yd. by 1 yd.), highly absorbent, and possessing considerable powers of capillary attraction. It is therefore employed as a primary wound-dressing to promote drainage of the exudates. For plugging sinuses and cavities, ribbon gauze (1/4 to 2 in. broad) with selvedges is used. Gauze may be medicated with Boric Acid 3 to 7%: Euflavine 0·1 to 0·2%; Iodoform 4 to 6%; Mercuro-Zinc Cyanide 0·5 to 1·5%; Picric Acid 2%. *Moist Gauzes* contain 1 to 5% of Glycerin. Cotton-Wool enclosed in gauze is made into suitable shapes and sizes to form swabs, pads, abdominal sponges, shell dressings, etc. *Gamgee Tissue* is Cotton-Wool enclosed in gauze, plain or medicated; jackets ("pneumonia jackets") made of Gamgee Tissue are used to prevent chill in fevers, but, as Cotton-Wool does not allow moisture to escape, pure animal wool has been suggested in its place. *First Field Dressings* consist of two gauze pads, 4 by 3 in., impregnated with 0·1% Proflavine, and sewn 18 in. from one end to a cotton bandage; they are enclosed in parchment paper, jaconet and an outer khaki cotton cover.

Lint, Absorbent or Surgeons'.—A closely-woven cotton fabric, the fibres on one side being carded. It is not a good absorbent, but is used as a dressing for superficial wounds and as a medium on which to spread ointments or on which counter-irritants are applied to the chest, etc.; and lint or flannel, wrung out in hot water and sprinkled with Turpentine, is termed a turpentine stupe. *Boric Lint*, 5% Boric Acid, is employed after moistening with water as an antiseptic poultice, or dry as a protective for slight wounds. *Euflavine Lint* contains 0·1% Euflavine.

Sphagnum Moss, the stems and leaves of various bog-mosses, freed from foreign matter and dried, is highly absorbent, elastic, and to some extent a deodorant. In War time, it was employed loose as an absorbent of fæcal and urinary discharges, or covered with muslin in pads, which were used in place of cotton-wool.

Tow, Surgeons', consists of the finer fibres of teased jute. It is not a good absorbent, and is employed mainly to collect fæcal and other septic discharges. *Carbolized Tow* is also prepared. Jute and Carded Oakum (Marine Lint) are occasionally used.

Felt is used to apply moist heat and counter-irritants to the skin. *Spongio-piline* is thick felt waterproofed on one side.

Waterproof Dressing Materials.—Gutta-percha tissue, jaconet, battiste, oiled rayon or silk and christia tissue are placed above moist dressings to prevent escape of moisture. Tulle Gras or Paraffin Gauze Dressing is gauze impregnated with Yellow Soft Paraffin and Balsam of Peru. *Cargile Membrane* is an animal membrane employed to prevent the occurrence of adhesions between two tissues after operations.

Bandages are generally made of loosely-woven cotton, calico or flannel, in widths of 1 to 6 in.; occasionally they are medicated. Adhesive rubber plaster tape, including elastic forms, can be used instead. Plaster bandages, made by impregnating muslin, crinoline or loose-woven bandages with (80%) exsiccated Calcium Sulphate, are used to secure immobility of the limbs or spine, but a flannel bandage should first be applied next the skin. Crepe bandages are so woven that they possess elasticity, and are used like india-rubber and elastic adhesive bandages for support to varicose veins, etc.

MASSAGE AND REMEDIAL EXERCISES

The application to the surface of the body, by either manual or instrumental means, of kneading, rubbing, stroking, etc., is termed "Massage." In treatment, massage is nearly always used in conjunction with remedial movements, either active or passive, the effects of which are supplementary to those of massage. The various movements are applied in the following methods:

1. **Stroking.**—Effleurage—is the term applied to the act of stroking the skin in a centripetal direction from the peripheral to the central parts of the body by the tips of the fingers, the ulnar edge of the hand, or the palm; occasionally centrifugal stroking is used for the relief of pain. Effleurage is soothing and analgesic; it promotes the return flow of blood by the veins and increases absorption of effusions by the lymphatics.

Uses.—In treating recent fractures to relax the muscular spasm, and in nerve injuries, neuritis, sciatica, neuralgia and frost-bite, in which more vigorous massage would do harm. Cases of persistent insomnia are relieved by gentle massage, and the intestinal movements may be stimulated by this means.

2. **Friction** is the term given to the circular rubbing movements applied with pressure by the thumb or finger-tips. Friction is definitely stimulant; it results in acceleration of the local circulation, softening of indurated tissues and more rapid absorption of effusions. As a lubricant to the skin, dusting powder, vaseline or oil may be applied.

Uses.—In the treatment of sprains, contusions, adhesions, synovitis, fibrositis, myalgia and muscular rheumatism. Scar tissue is softened and the stiffness of joints relaxed; and, after the acute stages have passed, it may be used to promote absorption of effusion in fractures and arthritis. Chronic rheumatoid arthritis and gout are sometimes benefited. Through its effects on the circulation, friction serves to maintain the nutrition of the muscles during convalescence from poliomyelitis, spastic paraplegia and hemiplegia; it has been recommended for Raynaud's disease.

3. **Kneading.**—Petrissage—consists in raising the tissues, skin and muscles, and kneading them between the fingers, or in applying rolling movements to a limb held between the hands.

Uses.—Kneading is largely employed in softening the cicatricial tissue of wounds; it prevents atrophy in muscular paralysis due to anterior poliomyelitis, and improves the muscular tone when disuse has led to atrophy. Abdominal massage by kneading is valuable in chronic constipation due to colonic stasis and in mucous colitis; it also improves the portal circulation.

4. **Percussion.**—Tapotement—implies repeated striking movements applied with the finger-tips—*punctation*; the inner aspect of the hand—*hacking*; the palm—*clapping*; or the fist—*beating*. Varying with the strength of percussion, the nerves, muscles and local circulation are stimulated.

Uses.—Mainly in the treatment of various forms of muscular paralysis or atrophy when the cases have improved under less vigorous treatment, and in the relief of fatigue and stiffness after unusual physical exertion.

5. **Vibration** may be conveyed to the tissues by the fingertips or palm, but a more satisfactory method is by the use of vibrating machines which admit of the speed and intensity of the vibrations being altered; the intensity is usually varied by using hard and soft applicators.

Uses.—Weak vibrations are sedative and may be employed to relieve pain from nerve injuries, neuritis, neuralgias, etc. Strong vibrations are stimulant and are used like vigorous massage to soften scar tissue, and in treating muscular rheumatism.

These various forms of massage are commonly used *seriatim* in treating a single case; it is usual then to finish by a return to stroking.

6. **General Massage** is applied by stroking, friction and kneading over the whole body, taking in rotation the lower limbs, arms, neck and chest, abdomen, and finally the back. According to the degree of pressure employed, the effects may be sedative or stimulant. Passive movements of the joints are carried out *seriatim.*

Uses.—Where the patient is too weak to take any form of exercise, in debility, insomnia, anæmia, convalescence, and neurasthenia. In heart disease and obesity it is valuable, and in bedridden patients it sustains the nutrition of the muscles.

MOVEMENTS AND EXERCISES.—Movements may be of two varieties: (1) passive, (2) active.

1. **Passive movements** are performed on the patient by an attendant, the patient's muscles being completely relaxed. Gentle passive movements afford mild exercise for the joints and the muscles connected with them.

Uses.—They are employed in treating injuries or stiffness in joints unless a ligament has been ruptured; in exercising the joints in fractures of the long bones; and after the acute symptoms have subsided in arthritis. Passive movements are also used to break down adhesions and increase the range of movement in joints where movement is limited as the result of injury or disease.

2. **Active movements** are carried out in the form of simple physical exercises—Swedish Drill, or other systems of muscular training. They may be subdivided into two groups:

(*a*) GRADUATED EXERCISES.—These are so regulated and increased by degrees that the patient is at no time conscious of physical strain. Such exercises are advantageously followed by massage and then complete rest. Graduated and re-education exercises are important treatments in the convalescent stage of diseases, but it is essential that the effect of these exercises should be watched so that strain, even against gravity, may be avoided. They are of value in cardiac and respiratory diseases, e.g. cardiac failure and empyema, in which the value of *breathing exercises* must be borne in mind. A further extension of graduated exercise consists in progressive hill-climbing, provision for which is made at many hydro-therapeutic establishments. Graduated exercises requiring definite nervous concentration, such as balancing exercises and games, step-dancing, etc., are helpful in treating neurasthenic cases; co-ordination exercises are extremely valuable in splastic paraplegia and locomotor ataxy.

Uses.—In debility—particularly post-partum or post-febrile—in obesity, in anæmia, etc., in spinal curvature to improve posture, and in injuries to joints, nerves and muscles, as well as in the conditions mentioned above.

(*b*) RESISTANCE EXERCISES.—These are exercises carried out against external resisting force which may be either manual or instrumental, such as is given by machines of the Zander type and other orthopædic appliances. The resistance in such cases should be graduated, and in amount insufficient actually to impede the movement. When a muscle is so weakened that it is unable to perform its normal function, the limb may be moved passively and the patient be directed to resist the passive movement with the impaired muscle; the term "eccentric movements" is applied to this method of treatment. Resistance exercise of the respiratory muscles is practised by blowing fluid from one bottle into another.

Uses.—Resistance Exercises are most largely employed in the treatment of obesity and cardiac failure, and during recovery from articular, nervous and muscular injuries.

BATHS AND ALLIED MEASURES

The principles on which the uses of baths depend are in a great measure identical with those just discussed. The relations of the vessels and nerves of the skin to the body-heat, circulatory, respiratory and nervous systems, form the basis upon which Hydrotherapy and Balneology are established. Certain methods used in "home" treatment will first be described.

The cold bath in fever.—A simple tepid-water bath is prepared at a temperature of about 90° F.; the patient is carefully placed in it; and cold water is added until the thermometer in it falls to 80° F. or even

65° F., according to circumstances. Here the patient remains for ten to twenty minutes or, his temperature being taken during immersion, until the internal temperature falls to 101° F.; if shivering occurs, he is at once removed. He is then half-dried, placed in bed, and covered with blankets; usually the temperature falls by evaporation of moisture slightly after his return to bed. A stimulant may be required. As the effect is only temporary, the cold bath may be repeated several times a day if indicated.

It is particularly useful in enteric and other fevers when the temperature is persistently above 103° to 105° F.

The wet-pack.—Prepare a bed by spreading a mackintosh and a blanket on the mattress and over the pillow. Wring out a linen sheet with cold water, and spread it smoothly over the blanket short of the pillow. Strip the patient, place him on his back on the sheet with his head on the pillow, and envelop him in the sheet and blanket by bringing these, one side at a time, across his body, and tucking them under the opposite side and under the heels. Finally, cover him with several more blankets, and again tuck these closely round him. The ordinary duration of packing is a quarter of an hour to an hour. The pack is then removed, and the skin rubbed with a dry towel. The pack may be repeated several times a day if necessary.

The sense of chilliness produced by the wet sheet is quickly replaced by a comfortable glow. The first action of the wet-pack is chiefly refrigeration of the skin; heat is abstracted so that the temperature quickly falls. Afterwards, the pulse is often slowed and increased in force, respiration is less frequent and restlessness relieved, so that sleep is often induced. The second effect of the wet-pack is diaphoresis, which may be profuse, the body being practically in a vapour bath. This is increased by sipping *cold* water during the pack.

Water Baths.—Apart from their importance for personal cleanliness, the effect of water baths is dependent upon their temperature. A cold bath (32° to 60° F.) cools the surface of the body and reflexly stimulates the heart, respiration and mental faculties, hence it is spoken of as refreshing. An exhilarating sensation of warmth should follow after the bath; too long immersion may cause chill. A cool bath (60° to 70° F.) has similar but less marked effects. Tepid baths (85° to 95° F.) lower febrile temperature, are soothing to the sensory endings and often induce sleep. Warm or hot baths (95° to 100° F.) raise the cutaneous temperature, dilate the skin vessels and promote profuse perspiration. They are used as diaphoretics in fever and in uræmia and have also a soporific effect. Local hot baths are used to increase circulation in the part immersed.

Vapour Baths.—The vapour or Russian bath at a temperature of 95° to 110° F. has effects similar to those of hot-water baths and is used as a diaphoretic measure.

Air Baths.—The hot-air or Turkish bath consists of a warm room, "tepidarium" (110° to 130° F.), in which the patient commences within fifteen minutes to perspire freely; he may then transfer to the hot room, "calidarium" (150° to 200° F.), for a few minutes until vigorous perspiration is induced. He then enters the cooling room, where the body is shampooed to remove all perspiration and finally receives a cool shower or plunge bath. The Turkish bath is essentially a diaphoretic treatment which is regarded as stimulating metabolism, and is recommended in obesity, uric-acid diathesis, fibrositis, lumbago, chronic rheumatism, etc. Localized joint affections of rheumatic type are treated by local hot-air baths. Electric heat or radiant heat baths which employ carbon filament lamps as the source o f heat are largely utilized for the same purpose.

Medicated Baths.—Baths containing the salts of sea-water have been regarded as specially invigorating, but this conclusion is doubtful. Sulphide baths are recommended in chronic rheumatic conditions; and mud, pine, and bran baths are also advised but on dubious grounds. Baths containing Calcium Chloride and Carbon Dioxide (Nauheim baths) have a doubtful value in the treatment of myocardial weakness.

MINERAL WATERS—SPAS

Natural Mineral Waters available for therapeutic purposes are commonly classified by their most important chemical and physical characters respectively—water, salts, gases, their temperature and their radio-activity. It must be noted, however, that most of them are very complex in composition, and that the different classes merge in each other, certain salts, particularly Sodium Chloride, being common to many. It follows that a name given to a class from an important constituent, e.g. "Sulphur Waters," does not exactly express its action. Nor can the effects and value of a water be fully accounted for by the sum of the individual actions of its constituents, the precise chemical combinations of the various ions being uncertain. Again, the action of water itself is considerable, and differs with its amount, temperature and mode of application. Further, at all spas, valuable influences besides the chemical and physical properties of the waters are at work on the patient, namely climate, rest, "change," diet and amusements. Accordingly, the uses of the different mineral waters are still partly empirical and those of each class will be stated briefly, together with the diseases in which they are stated to be useful.

METHODS OF EMPLOYMENT

I. EXTERNAL TREATMENT. (1) *Simple "long" baths.*—The patient lies immersed in the water at a suitable temperature for a specified time; is removed, wrapped in a warm sheet and blanket, and rests for 30 to 40 minutes; and is then cooled gradually in a special room.

(2) *Douches.*—A strong stream or spray of water at a proper temperature, from a hose regulated by the attendant, plays upon the body or a special part for several minutes.

(3) *Douche-Massage; Aix-Douche.*—The patient, or a particular joint, is *massaged* under a full stream of warm water from a rose spray finishing with a douche. *Vichy-Douche.*—The patient, lying flat, is massaged under three or four rose sprays from an overhead bracket.

(4) *Needle Spray.*—This is a vertical cage of pipes pierced internally so as to give a shower effect over the whole body.

II. INTERNAL TREATMENT: DRINKING.—The amount, temperature, frequency, hours of drinking, and other circumstances, such as relation to meals and (occasional) addition of varying medicinal salts to the water, are ordered by the hydropathic physician.

CLASSES, WITH THE MORE IMPORTANT SPAS

1. **Simple Thermal Waters—Warm** or **Hot Waters.**—With elevated temperature but only small percentages of solids.

BRITISH.—Bath, 120° F.; Buxton, 82° F.; Mallow, 70° F.; Matlock, 68° F. NEW ZEALAND.—Rotorua. U.S.A.—Many hot springs. FRANCE.—Aix-les-Bains, 86–120° F., with H_2S; Plombières, 77–165° F.; Dax, 127–140° F.; Bagnoles-de-l'Orne, 81–84° F. GERMANY.—Wildbad, 91·5–104·5° F. ITALY.—Lucca, 100–129° F.; Bormio, 90–104° F. SWITZERLAND.—Ragatz, 96° F.; Leuk, 102–124° F., calcareous. CZECHOSLOVAKIA.—Teplitz, 95–120° F.

Uses. Externally: In skin diseases, rheumatic and gouty arthritis, sciatica and lumbago, chronic pelvic disorders in women, functional nervous disorders, neurasthenia. *Internally*: In chronic gastric and intestinal disorders.

2. **Calcareous Waters.**—Contain Calcium Sulphate, Chloride, Carbonate, and Magnesium Carbonate. Some thermal.

BRITISH.—Bath, 120° F.; Leamington; Buxton, 82° F. U.S.A.—Many. FRANCE.—Contrexéville, St. Galmier, Vittel, Bagnères-de-Bigorre. GERMANY.—Wildungen, Nauheim. SWITZERLAND.—Leuk, 102–124° F.

Uses.—Externally: As thermal waters and in cardiac disease. *Internally:* In diseases of the urinary tract, particularly gravel and calculus.

3. **Saline Waters, Common Salt Waters.**—Contain mainly Sodium Chloride with other Chlorides, Carbonates, Sulphates or Sulphides; and CO_2 Gas.

BRITISH.—Droitwich, Nantwich, Woodhall Spa, Leamington, Cheltenham, Harrogate, Llandrindod, Llangammarch. FRANCE.—Salies-de-Béarn, Brides-les-Bains, Bourbonne-les-Bains. ITALY.—Salsomaggiore, Ischia, thermal (140° F.), Castellamare. SWITZERLAND.—Bex. GERMANY.—Homburg, with CO_2; Kissingen with K and Li; Kreuznach; Nauheim, thermal (82–95° F.), with CO_2; Wiesbaden, thermal (100–156° F.); Baden-Baden, thermal (125–150° F.), with Li, radioactive. U.S.A.—Many.

Uses.—Externally: In chronic rheumatic affections, cardiac diseases, skin diseases, as local and general tonics like sea-water baths. *Internally:* In chronic gastric and intestinal diseases, constipation, gout, rheumatism.

4. **Sulphated Waters, Aperient Waters.**—Contain Sodium and Magnesium Sulphates; some with Sodium Chloride; some with Alkaline Carbonates or Sulphides.

BRITISH.—Leamington, Cheltenham, Strathpeffer, Matlock, Droitwich. FRANCE.—Brides-les-Bains, muriated. BELGIUM.—Bertrich, thermal (90° F.) HUNGARY.—Æsculap, Hunyadi, Apenta. SPAIN.—Rubinat. Condal. GERMANY.—Friedrichshall, Carlsbad, thermal (102–163° F.), Marienbad, Franzensbad, Püllna. SWITZERLAND.—Tarasp, alkaline, with CO_2. U.S.A.—Many.

Uses.—Externally: Little used. *Internally:* In gastric and intestinal catarrhs, constipation, hæmorrhoids, hepatic disorders, gall stones, obesity, glycosuria, gout, gravel.

5. **Sulphur Waters.**—Contain Sulphides of Hydrogen, Sodium,

Potassium, Calcium, Magnesium. Cold or thermal; some with Sodium Chloride.

BRITISH.—Strathpeffer, Llandrindod, Harrogate, Llanwrtyd, Moffat. EIRE.—Lisdoonvarna. FRANCE.—Eaux-Bonnes, Eaux-Chaudes, Barèges, Bagnères-de-Luchon, Aix-les-Bains and Cauterets (all thermal); Challes. ITALY.—Acqui, thermal. SWITZERLAND.—Leuk, thermal. GERMANY.—Aix-la-Chapelle, thermal. EGYPT.—Helwan, thermal. NEW ZEALAND.—Rotorua, thermal. U.S.A.—Several.

Uses.—Externally: As simple thermal waters. *Internally:* In constipation, hepatic disorders, chronic diseases of joints and skin, and respiratory passages. *As Inhalations:* In chronic pharyngeal and respiratory catarrhs.

6. **Alkaline Waters.**—Rich in Sodium Carbonate; also Magnesium, Calcium, and occasionally Potassium, Lithium, Barium, and Strontium Carbonates; Sodium Chloride; and CO_2 Gas in relatively large proportion.

BRITISH.—None pure. Mainly compound—Harrogate, with Sulphur; Buxton, with Radium; Matlock. FRANCE.—Vichy, thermal (108·5° F.), with CO_2; Mont Dore, thermal (108–113° F.), with CO_2 and As; Vals; Évian; Royat, thermal (68–95° F.), with Chlorides; Bourboule, thermal (130° F.), with Chlorides and As. GERMANY.—Ems, thermal (80–120° F.), with Chlorides and CO_2; Apollinaris, with CO_2; Neuenahr, thermal, with CO_2; Selters, with Chlorides. Bilin, with CO_2. SWITZERLAND.—Tarasp, sulphated, with CO_2; St. Moritz, with Fe and CO_2. U.S.A.—Several. NEW ZEALAND.—Te Aroha.

Uses.—Externally: Cleansing, tonic. *Internally:* In indigestion, hepatic disorders, gall stones, uric-acid diathesis, pelvic diseases. *As Inhalations:* In laryngeal and bronchial catarrhs and asthma.

7. **Chalybeate Waters.**—Contain Iron (1) as *Carbonate.* BRITISH.—Harrogate, $FeCO_3$, 0·0147%, with Sulphur; Bath, $FeCO_3$, 0·002%, thermal, with Calcium; Strathpeffer, with S. Most British Mineral Waters contain traces of Iron Carbonate. (2) As *Sulphate.*—Trefriw, 0·395%: Flitwick 0·244%. BELGIUM.—Spa. SWITZERLAND.—St. Moritz, with free CO_2. GERMANY.—Schwalbach and many others, variously with Sulphates, Chlorides, Alkalis and CO_2. ITALY.—Levico and Roncegno, with Arsenic.

Uses.—Externally: As simple thermal Waters with free Carbonic Acid. *Internally:* In convalescence from anæmia and diseases causing it or due to it.

8. **Special Waters.—Potassium Waters.** BRITISH.—Bath, Buxton, Woodhall, Llandrindod. FRANCE.—St. Galmier, Contrexéville, Vichy. SWITZERLAND.—Tarasp, Bex. GERMANY.—Kissingen, Ems, Carlsbad, Bilin, Wildbad, Neuenahr. *Uses* (*see* p. 47).

Lithium Waters. BRITISH.—Bath, Llandrindod, Llangammarch. FRANCE.—Royat, Bourbonne-les-Bains. GERMANY.—Baden-Baden. *Uses* (*see* p. 49).

Bromine Waters. BRITISH.—Woodhall Spa, Llangammarch, Nantwich. ITALY.—Salsomaggiore. *Uses* (*see* p. 125).

Iodine Waters. BRITISH.—Woodhall Spa. FRANCE.—Challes. ITALY.—Salsomaggiore. *Uses* (*see* p. 118).

Radio-active Waters. BRITISH.—Harrogate, Bath, Llandrindod, Buxton, Matlock, Droitwich. CONTINENTAL.—Several.

BRITISH SPAS AND THEIR PRINCIPAL CONSTITUENTS

Bath.—Thermal, 120° F.; Calcareous, $CaSO_4$ 0·146%, $CaCO_3$ 0·012%; with Na_2SO_4, $MgCl_2$, Li and K; radio-active.

Buxton.—Thermal, 82° F.; with $CaCO_3$, $MgCO_3$ NaCl, K, and Ba; free N and CO_2; radio-active. Altitude 1,000 ft.; bracing.

Cheltenham.—Sulphates and Chlorides—Na_2SO_4 0·22%, $MgSO_4$ 0·16%, NaCl 0·66%; alkaline Carbonates—Mg, Ca and Na.

Droitwich.—Common Salt—NaCl 30·7%; Sulphates—Na_2SO_4 0·48%; radio-active.

Flitwick.—Chalybeate—$FeSO_4$ 0·244%.

Harrogate.—Sulphur—H_2S 3·76 c.c.%, and Na_2S; CO_2 14·4 c.c. %; NaCl 1·27%; with Ba, Sr, etc.; radio-active. Altitude 600 ft.; dry, bracing.

Leamington.—Sulphates—Na_2SO_4 0·146%, $MgSO_4$ 0·085%; Chlorides—NaCl 0·97%.

Lisdoonvarna (Eire).—Sulphur—H_2S 0·4 c.c. %, with free CO_2.

Llandrindod.—Sulphur—H_2S 0·94 c.c. %; Chlorides—NaCl 0·232%, with Li; radio-active.

Langammarch.—Chlorides—NaCl 0·266%; with $BaCl_2$ 0·01%.

Llanwrtyd.—Sulphur—H_2S 3·6 c.c. %; Chlorides—NaCl 0·086%; with traces of Li, Ba, I, and Br.

Mallow.—Thermal, 70–72° F.

Matlock.—Thermal, 68° F.; Sulphates—$MgSO_4$ 0·0139%; with $CaCO_2$ and free CO_2; radio-active.

Moffat.—Sulphur and chalybeate springs.

Nantwich.—Common Salt—NaCl 20%, with KBr 0·0024%.

Strathpeffer.—Sulphur, H_2S 6·8 c.c.%; Na_2S 0·0031%; CO_2 13·8 c.c.%; Sulphates—Mg and Na 0·0639%.

Trefriw.—Chalybeate—$FeSO_4$ 0·395%.

Woodhall.—NaCl 2%; with KI 0·0007% and KBr 0·005%.

ELECTRO-THERAPEUTICS

The following summary is not intended to be more than a guide for the student to the application of electricity in therapeutics. Reference must be made to textbooks on the subject for fuller information.

Galvanic Current.—During the passsage of the galvanic current the excitability of nervous tissue is increased in the region of the cathode and decreased in that of the anode. For local treatment a current of 5 to 10 ma., increasing with the size of the electrode, is usually employed for about ten minutes at a sitting. The stimulant effect of the cathode is used in weakness and paralysis of nerves or muscles; the sedative effect of the anode is employed in painful and spasmodic diseases, e.g. neuralgia, sciatica, and various neuroses. Galvanic shocks, conveniently given by means of a metronome interrupter, are useful in stimulating wasting muscles. Surging Galvanic Currents, in which half a second elapses between the zero and maximum, cause contractions only of muscles showing reaction of degeneration; slowly alternating Galvanic Currents have the same action. Total-immersion baths are now replaced by Schnee's four-cell bath, in which the amount of current passing through the patient can be more accurately measured. *Condenser Dis-*

charges are an exceedingly useful method of applying stimuli to muscles or nerves; the exact discharge can be measured and progress estimated by observing the minimal condenser capacity necessary to evoke contraction. The Galvanic Current is employed in the treatment of debility, neurasthenia, muscular rheumatism, and subacute neuritis. For the removal of superfluous hair, electrolysis is satisfactory; a current of 2 ma. for 5–10 seconds is used, and the negative electrode is a needle inserted along the hair follicles which are destroyed.

Faradic Current.—This is employed mainly as a stimulant to muscular tissues; the objection to its use is the uncertain speed of the interruptions in small coils and the suddenness and irregularity of the alternations of potential, which cause pain. Coils are designed to overcome these defects. Faradism is employed locally in the treatment of paralyses and to maintain muscular tone.

Sinusoidal or Alternating Current.—This has the advantage that the change of potential takes place gradually and regularly instead of suddenly; hence shock and pain are avoided. The quick Sinusoidal Current contracts normal muscles but not those showing reaction of degeneration and is used in muscular weakness following illness or injury.

Diathermy.—By means of special apparatus High-Frequency Currents (1 to 3 million oscillations per second) of low voltage but high amperage can be utilized for the production of heat. The sensation of heat is felt not only at the point of contact but in parts between the electrodes; thus artificial fever can be produced, circulation and respiration are stimulated, sweating induced and pain relieved. Diathermy has been employed to relieve pain caused by inflammatory processes, neuralgias, arthritic conditions, fibrositis and myalgias. Applied over the chest it will cause a fall in blood-pressure and has been used in hyperpiesia, and on account of its general effect of increasing body-temperature it has been utilized to cause artificial pyrexia in the treatment of general paralysis. By concentrating these currents through metal electrodes on a small area the density of the current may be increased so as to destroy the tissues; simple or malignant neoplasms, tuberculous or septic tissues can thus be removed without much hæmorrhage, due to the coagulation and sealing of the vessels by diathermy; thus the danger of infection of healthy parts is avoided.

Short-wave diathermy, using 10–50 million oscillations per second to produce a wave-length of 6–35 metres, can be used to induce artificial pyrexia or local effects by placing the patient or the part affected in the electrostatic field between two condensers; it is displacing the older diathermy and treatment can be done without removal of clothing.

Faradic Treatment of Obesity (Ergotherapy).—Applying the principles of diet and exercise to the treatment of obesity, Bergonié has substituted for active exercise rhythmic muscular contractions induced by the faradic current and resisted by sand-bags placed over the muscles stimulated. The treatment is painless, and applications are given once or twice daily for 15 minutes, increasing to 60 minutes at the end of treatment. Fatigue is obviated, respiration is deeper, the pulse is more frequent but less so than from physical exercise. The loss of weight averages 500 G. per day.

X-Rays.—These rays have been used in treatment because their properties are such that in small doses they decrease the activities of the superficial glands (sebaceous glands, etc.). In larger doses they cause hyperæmia and, if prolonged, destruction of the tissues. For these reasons they can be used in small doses in the treatment of acne, hyperidrosis, etc., in larger doses for chronic skin conditions, and in still larger doses to destroy neoplasms.

Their action can be localized to specific areas by means of cones with protection of the surrounding skin, and their effect can be accurately measured by their power of ionization. The unit of dosage is expressed by the international "r" unit which is an absolute unit of ionization. The degree of penetrability of the rays is controlled by the kilovoltage, the higher the kilovoltage the shorter the rays and the more penetrating the radiation. In order to produce homogeneity of the beam and increase penetration, filters of copper and aluminium are used between the port of entry of the rays and the source of emanation. Filters vary in thickness from 1 mm. of aluminium to many mms. of copper, and the kilovoltage varies from 40 Kv (Grenz) for skin lesions, to ten million Kv. for deep-seated malignant lesions, the rays reaching the lesion through several ports of entry so that they may be concentrated at the lesion without damage to the superficial tissues.

Soft or superficial X-rays are used in the treatment of acne, chronic dermatitis, prurigo, pruritus, lichen planus and boils. They are used also in chronic eczema, hyperkeratosis, verrucas and lupus. Penetrating radiations are used in the treatment of carcinoma and sarcoma, particularly for the glandular extension. They are used in the control of leukæmias and reticuloses, and to depress the activity of the thyroid. They can also be used in menorrhagia to destroy the sensitive germinal cells of the ovaries.

Radiant Heat.—The part affected, or the whole body, is placed within a reflecting case provided with a large number of electric lights. The light is stimulating, causes free perspiration, and augments the cutaneous circulation. Radiant heat is used in muscular rheumatism, chronic rheumatoid arthritis and other joint-affections. Dry hot air produces local hyperæmia, and hot-air baths relieve sciatica and the joint pains of chronic rheumatism. Certain types of heat elements and radiating surfaces give off a rich supply of infra-red rays and these now replace the ordinary heat elements. Infra-red rays penetrate well, cause local vaso-dilatation and are used in similar diseases and to treat boils and carbuncles.

Ultra-Violet Therapy, Heliotherapy.—Exposure of the skin to the ultra-violet rays 2,900 to 3,300 Å.U. produces bronzing from deposit of melanin in the skin; over-exposure, especially to rays of or below 2,900 Å.U. causes erythema, exfoliation of epithelium or even ulceration. Ultra-violet light in therapeutic doses appears to improve metabolism and vitality and to relieve mental fatigue; blood-pressure is slightly lowered. It has a powerful inhibitory effect on the development of rickets, by activating Provitamin D in the tissues; and also on lupus and tuberculous infections, not by a toxic action on the bacteria but by raising tissue-resistance. Local and general exposure of the body to the ultra-violet rays of sunlight either at seaside or high mountain resorts forms an important part of treatment in tuberculosis of joints and bones;

pulmonary tuberculosis may be activated by excessive exposure to sunlight but controlled dosage may be beneficial. *Artificial Sunlight* may be given locally or generally. For local application a lamp such as the Finsen-Reyn with quartz windows may be used; and for general application the carbon arc, with plain or metal-cored carbons, or mercury-vapour type, may be employed.

With a carbon arc consuming 25 to 30 amp., the exposure for the whole body is five minutes at 3 ft. distance; the time is increased by five minutes on alternate days until the patient is receiving about an hour's exposure daily; the eyes must be protected by shields or smoked glasses. Ultra-violet rays have proved valuable in indolent ulcers and wounds, tuberculous lesions of joints or bone, lupus, and many chronic skin infections.

Iontophoresis or Ionic Medication.—The electrical introduction into the superficial tissues of medicines in an ionized, nascent, actively combining form is painless. Penetration is proportional to strength of current and duration of flow. The immediate effect is purely local and superficial; the absorbed ions form salts in the superficial tissues but the amounts absorbed rarely produce general effects.

By electrolysis a substance is broken up into ions. Positively charged ions (*kations*) travel from the positive pole towards the negative pole. To introduce these they must be applied at the anode. Such are H, Na, K, Li, Mg, Cu, Zn, and alkaloidal bases, etc. Negatively charged ions (*anions*) pass from the cathode to the anode, and are introduced under the cathode; these are OH, Cl, Br, I, and Salicylate, etc.

Method of Administration.—The active electrode is covered with about 16 layers of absorbent lint, which is soaked in a solution of the electrolyte of the desired strength and placed on the affected part. The indifferent electrode, large, and soaked in Normal Saline, is applied to any convenient spot. The intensity of the current is varied with the size of the electrode: when small areas are treated, 10 to 18 ma. is sufficient, but with large areas and using a large electrode, e.g. the solution in an earthenware cell, the intensity may be increased to 90 or 120 ma.

Actions and Uses of Ions.—*Copper ions* (2% Copper Sulphate) are antiseptic in pyorrhœa alveolaris. *Iodine ions* (2% Potassium Iodide) reduce inflammation, and are used in muscular rheumatism. *Sodium Chloride* (1 to 4%), when applied at the cathode, softens fibrous tissues and cicatrices, and ameliorates ankylosis. The *Salicylic ion* (2% Sodium Salicylate) relieves the pain of neuralgias, acute articular rheumatism, rheumatoid arthritis and sciatica. *Zinc ions* (2% Zinc Chloride) are powerfully antiseptic and astringent; they are used in rodent ulcer, lupus, carbuncles and boils, and in septic diseases of the eyes, ear, nose, teeth, urethra and colon. *Magnesium ions* (2% Magnesium Sulphate) are valuable for flat warts.

RADIUM, Ra 226·4, & RADIUM BROMIDE, $RaBr_2$

Of the three kinds of Radium rays, the α rays, +-charged atoms, have little penetrating power. The β rays consist of — -charged electrons, identical with the cathode rays. They are more penetrative than α rays. The γ rays are analogous to X-rays. They are powerfully penetrating.

Actions and Uses.—The only rays now used in radium therapy are those of the γ range. These rays have a penetrating power equivalent to rays developed by 10–20 million volts and are lethal to tissues. The radium salt is sealed in platinum needles or containers, the metal acting as a filter to the softer rays and also protecting the salt against damage. The principle underlying the use of radium is dependent on the fact that radiation is lethal to all tissues, but whereas normal or specialized tissue has a certain degree of resistance or recoverability, this property is not developed in neoplastic tissue, therefore the dosage which would just fail to destroy normal tissue would prove fatal to malignant tissue. Consequently there is only a small margin between correct and overdosage.

As with X-rays the dosage is measured in the "r" unit and adequate dosage depends on an even radiation applied throughout the tissue. This has to be measured and applied on a physical basis. Three methods are available for treatment; the needles may be inserted in and round the growth, they may be applied to the surface of superficial lesions, or at some distance when used as a larger source of radiation (bomb). Radium emanation (sealed in small gold or platinum seeds) can also be used, but the period of activity of these seeds is limited; they lose half their original strength in 3·85 days. They can, however, be used in inaccessible places such as the pituitary, etc., and left *in situ* when they become inactive. Their laws of decay follow definite physical laws.

Radiation has now reached another phase in which it has been found possible to produce artificial radio-activity in certain salts by subjecting them to bombardment by the radium "pile" or cyclotron. Activated radio-active iodine has been used in the treatment of thyrotoxicosis by intravenous injection and radio-phosphorus for bone tumours with varying success, but the future will probably hold out much scope for these artificially irradiated drugs whose tissue selectivity is known and whose power of radiation can be limited. The scope of this type of therapy appears to be unlimited and more rational in such diseases as leukæmia and polycythæmia.

Radium is used superficially in the treatment of nævus and keloids, rodent ulcers, epitheliomata and squamous carcinomata, and internally in the treatment of carcinoma and sarcoma, either with or without surgery, the degree of success varying directly with the size of the lesion

OUTLINES OF INVALID DIET

THE importance of dietetics as a therapeutic measure is apt to be overlooked, but there are few diseases in which recovery cannot be hastened by some appropriate modification of the patient's diet, whilst in some conditions the prescription of a strict diet takes precedence over any other procedure which may be adopted. Careful regulation of the quality and quantity of the food taken must be regarded as essential in fevers, in disorders of the organs of digestion and assimilation, in diseases of metabolism such as diabetes, obesity, and gout, and in diseases of the organs of excretion.

Caloric Requirement.—In planning a diet, especially if it has to be maintained for any length of time, regard must be had to the energy requirements of the patient. When at rest a normal man needs, in order to maintain his weight, sufficient food to provide 25 calories per kilogram; if he follows a sedentary occupation he will require about 35 calories per kilogram, and if he does muscular work he may need as much as 60 calories per kilogram. The caloric requirement is increased in pyrexia.

Fasting.—When vomiting and diarrhæa are prominent symptoms at the onset of acute diseases of the stomach and intestine, it is advisable to withhold food for one or two days.

COMPOSITION OF FOODS.—Every diet is necessarily made up of various amounts of protein, carbohydrate, fat, salts, extractives and vitamins; tables showing the varied proportions in different foods are available for the preparation of suitable diets for diabetes mellitus. Each of these constituents will now be discussed in relation to the requirements of the sick person.

Protein is essential for the maintenance of life; for the repair of tissue waste not less than 0·5 G per lb. body weight is needed daily. Each gramme of protein yields 4·1 calories. Protein has the property of increasing the metabolic rate, known as its "specific dynamic action." In the process of digestion, protein is broken down into its constituent amino-acids. Such of these as are not required for tissue repair are deaminized in the liver prior to being used as a source of energy, and the nitrogen thus liberated is excreted as urea. It follows that excess of protein places an additional load on the kidneys which are the chief organs for excretion of nitrogenous products. Protein is available in several different forms. It is present in *milk* as caseinogen and lactalbumin. It is the chief constituent of *white of egg* and, as such, is one of the most easily digested of foods. *Meat* is an important source of protein, but, in addition to its protein content, it contains varying amounts of fat, fibrous tissue and extractives which necessitate its careful selection by the physician as to quantity, quality and mode of cooking. Lamb and veal are the most suitable form of meat for the invalid as they contain but little fibrous tissue. Pork is generally unsuitable and its high fat content delays its digestion. Meat is rendered indigestible by overcooking, cooking more than once, or salting. Roasting retains most of the constituents *in situ*: boiling removes a proportion of the extractives and salts. The solid organs, such as liver, kidney, pancreas and thymus (sweetbread), are readily digested provided they are well masticated, but they yield relatively large amounts of nucleic acid which is a precursor of uric acid. Tripe, the cleaned and boiled stomach and intestine of the ox, is rich in gelatin and is a readily assimilated form of nourishment. Rabbit muscle contains very little fibrous tissue and is practically devoid of fat.

Poultry and Game.—The fine muscle fibres, relative absence of fibrous tissue and agreeable flavour make these eminently suited to the requirements of invalids. High game should, however, be avoided.

Fish is commonly regarded as being more digestible than meat though much depends on the kind of fish selected and the mode of cooking. Fish with coarse muscle fibres, such as cod or ling, is less readily digested than fish with fine muscle fibres, such as plaice or sole. Fish with a high fat content, such as salmon or mackerel, is rarely suited to the invalid's requirements. Steaming or boiling is the most digestible mode of cooking.

Gelatin is derived by prolonged boiling of the collagen of fibrous tissue. It is a valuable source of energy and a protein sparer, but lacks certain essential amino-acids. It is frequently given to invalids in the form of calves'-foot jelly.

A high protein diet is often ordered in chronic nephritis with œdema, provided nitrogen is being well excreted; the large excess of urea formed exerts a diuretic action which results in the diminution of œdema. A diet with a relatively high protein content is sometimes given in gastric ulcer (Lenhartz diet) and in obesity. Raw or very lightly cooked minced meat is of value in some forms of chronic diarrhœa. It is important that high-grade proteins, or their constituent amino-acids, be given when the liver has been damaged by infectious or toxic substances. The intake of protein should be reduced in acute nephritis and in chronic azotæmic nephritis, and in intestinal disorders where excessive putrefaction is taking place. Proteins with a high nucleic-acid content should be especially avoided in gout.

In diseases where digestion is grossly defective, as in advanced cancer of the stomach, milk, eggs or meat may be peptonized or pancreatized before their administration.

Carbohydrates are important sources of energy and are essential for the complete metabolism of fat. Each gramme yields 4·1 calories. Their utilization in the body requires the presence of adequate amounts of Insulin which is elaborated in the Islets of Langerhans of the pancreas.

The simplest carbohydrates are the *sugars* which are represented in the normal dietary principally by Sucrose. Lactose and Maltose are occasionally substituted for Sucrose, especially in infants; the former is less sweet than Sucrose; the latter has a slightly laxative effect.

Farinaceous foods enter largely into the invalid dietary. Such are arrowroot, semolina, cornflour and ground rice. All these are readily digested and are very completely absorbed. *Bread* is easily digested provided it is taken in conjunction with other foods. Its thorough mastication is promoted by toasting. Wholemeal bread contains considerably more salts and cellulose than white bread and is of value in constipation.

Vegetables vary considerably in their nutritive value, which is proportional chiefly to their starch and sugar content. Most of them contain considerable quantities of cellulose, which is indigestible and liable to undergo decomposition with the production of gas in the large intestine. They are a valuable source of inorganic salts and the legumes have also a considerable protein content. The boiling of vegetables ruptures the cellulose envelopes and thus liberates the digestible constituents.

Fruits such as grapes, plums, peaches and pears, as sources of carbohydrates, are usually much appreciated by invalids because of their agreeable flavour and property of relieving thirst. Only the soft portions should be eaten: the pips and skins are not digested and are liable to cause dyspepsia.

Carbohydrates are given liberally in the form of flours, bread, potatoes, etc., in states of under-nutrition or where hard muscular work has to be performed. Barley sugar is frequently given to children who are subject to attacks of acidosis. Carbohydrates need to be curtailed drastically in diabetes and in obesity; potatoes and the cereals are usually forbidden entirely, while other vegetables are classified according to their carbohydrate content and only those with 5 or 10 per cent. of available carbohydrate are allowed. Potato is contra-indicated in dyspepsia unless mashed or passed through a sieve and taken in the form of a thick vegetable soup. Green vegetables and fruit are allowed in constipation as their indigestible residue stimulates peristalsis, but they should be avoided in dyspepsia and diarrhœa or where intestinal fermentation is taking place.

Fats have a high energy value and yield 9·3 calories per gramme. They are digested and absorbed in the small intestine and delay the gastric digestion of other foodstuffs. They require the presence of carbohydrate for their complete metabolism. Fats of animal origin, such as butter, cream, egg yolk and Cod-Liver Oil, are vehicles for the fat-soluble vitamins, which are absent from the vegetable fats, olive oil and margarine (unless specially added). Cream is the most easily assimilated form of fat owing to its high degree of emulsification.

Fats are given liberally in under-nutrition. They are of value when given before meals, in hyperchlorhydria and peptic ulcer, as they inhibit the flow of gastric juice. Fats need to be curtailed in obesity but limitation of carbohydrate is of even greater importance in this condition. In diabetes mellitus, though they are a valuable source of energy, the quantity, in which fats can be allowed safely, is limited by the amount of carbohydrate which can be metabolized. Fats are contra-indicated in gall stones and nephrosis owing to the presence of hypercholesterinæmia in these conditions.

Salts.—The provision of adequate amounts of the different salts entering into biological processes is rarely a matter of any difficulty since they are present in most foodstuffs. Calcium and Iron are, however, occasionally deficient and a liberal allowance of meat and green vegetables requires to be given in order to ensure sufficient supplies in the diet.

Milk is a complete food and is almost ideal in fever and other debilitated states. It contains 3 per cent. of protein chiefly in the form of caseinogen which, in contact with gastric juice, forms coarse masses of casein. By the addition of 1 gr. of Sodium Citrate to each fluid ounce of milk, this clotting can be delayed and, when it ultimately occurs, the resulting flocculi are much finer and more readily digested. Milk contains 4 per cent. of lactose and 4 per cent. of fat (cream). It also contains 0·7 per cent. of inorganic salts including 0·15 per cent, of Calcium. The Iron content is, however, low, and for this reason milk cannot be given indefinitely without the development of anæmia. In certain gastro-intestinal disorders, milk is not tolerated as such: in these circumstances it may be diluted with water or soda-water; skimmed in order to diminish its fat content; or, by the addition of rennet or white wine, the caseinogen may be removed, leaving whey which consists chiefly of lactose, lactalbumin and salts as the final product.

The **vitamins** have already been adequately discussed (*see* p. 187).

Extractives comprise chiefly the purin bodies and creatinine; these are contained in meat and meat products such as broths, beef-tea, and meat extracts. They are stimulants which excite the flow of gastric juice and raise the blood-pressure. They are, therefore, of value in debilitated states, but should be avoided in kidney diseases, high blood-pressure, gout and hyperchlorhydria.

Beverages.—Tea, coffee and cocoa owe their refreshing properties to methyl purins, which produce effects resembling those of the extractives of meat. Tea in particular, and especially if it is of poor quality or has been infused for long, contains tannic acid and should therefore be taken sparingly in dyspepsia.

Aerated drinks have on the gastric mucous membrane a stimulant effect which is of value in the anorexia of fevers and other debilitated states.

The dietetic uses of Alcohol have been noted on p. 270.

AMOUNT AND FREQUENCY OF DIET

The amount and frequency of invalid meals, arranged together, vary widely with the disease, the age, sex and habits of the patient, and the kind and form of the food. The smaller the quantity that can be borne of a regular fluid meal, the shorter must be the interval between the supplies or feeds. The larger the allowance of a solid meal, the less frequently the meal is given. Hospital Dietaries include three ordinary diets:

No. 1. *Fluid or Fever Diet.*—Total, 60 fl. oz. Milk 40 fl. oz. Beef-tea 20 fl. oz.: 5 fl. oz. every two hours day and night; two feeds of Milk to one of Beef-tea. This is as much as can be borne, but of far less food-value than diet in health; and eggs or sugar or fine starchy foods are often added. In cases of prostration or of gastric irritability the intervals are still shorter, say, half an hour, and the amount given measured by teaspoonfuls.

No. 2. *Middle or Light Diet.*—Total 16½ oz. of solids and 3⅛ pints of fluid at five regular mealtimes, namely: *Breakfast*— Bread 3 oz., Butter ½ oz., Sugar ½ oz., Tea ⅛ oz., Milk 5 fl. oz. *Lunch*—Milk 15 fl. oz., Bread 1½ oz. *Dinner*—Soup 20 fl. oz., Bread 3 oz., Milk Pudding 5 oz. *Tea*—Bread 3 oz., Butter ½ oz., Sugar ½ oz., Tea ⅛ oz., Milk 5 fl. oz. *Supper*—Milk 15 fl. oz., Bread 1½ oz.

No. 3. *Full Diet.*—Total, 31 oz. of solids and 2 pints of fluid; consisting of Meat, Bread, Butter, Sugar, Milk, Soup and Potatoes.

DANGEROUS DRUGS ACTS, 1920, 1923, 1925, 1932, AND ORDERS IN COUNCIL, 1937, 1946, 1947 and 1950

THESE Acts regulate the import, export, manufacture, sale and use of Opium, Morphine, Cocaine, Cannabis Indica and derivatives of these. The prescriber should know the provisions of the Acts which concern him in the possession and use of these drugs.

The Acts apply to Opium, Morphine, its salts and esters, and any preparation containing 0·2 per cent. or more of anhydrous Morphine; Cocaine, Ecgonine, their salts, or any preparation containing 0·1 per cent. or more of the alkaloidal bases; Diacetyl-morphine (Diamorphine or Heroin), its salts and preparations; Dihydrohydroxy-codeinone (Eucodal), Dihydro-codeinone (Dicodide), Dihydro-morphinone (Dilaudid), Acetyldihydro-codeinone (Acedicone), Dihydro-morphine, their esters and salts; and of their esters Morphine-N-oxide (Genomorphine), the Morphine-N-oxide derivatives and other pentavalent nitrogen morphine derivatives: Amidone (Disephonine or Physeptone), Isoamidone, Dihydrodesoxy-morphine (Desomorphine), Methyldihydro-morphinone (Metopon), Pethidine and Hydroxypethidine and their salts; Thebaine and its salts, Benzyl-morphine, the other ethers of Morphine and their salts; Alphaprodine, Betaprodine, Ketobemidone, Methadol, Methadyl Acetate, and Phenadoxone (Heptalgin), their salts and preparations; Indian Hemp (Cannabis Indica), its resins, Extract and Tincture and any preparation, except one capable of external use only.

Certain preparations, although within the Acts, are exempted from the regulations; these include amongst others: Cereoli·Iodoform, et Morph.; Cocaine Eye Drops; Elixir Diamorphine. et Terpin. c. Apomorph.; Emplast. Opii; Linct. Diamorphin. Camph.; Linct. Diamorphin. c. Ipecac.; Linct. Diamorphin. et Scill.; Linct. Diamorphin et Thymi; Lin Opii; Lin. Opii Ammon.; Pasta Arsenicalis; Pil. Digitalis et Opii Co.; Pil. Hydrarg. c. Opio; Pil. Hydrarg. c. Cret. et Opii; Pil. Ipecac. c. Scilla; Pil. Plumbi c. Opio; Pulv. Cret. Arom. c. Opio; Pulv. Ipecac. et Opii; Mixtures of Pulv. Ipecac. et Opii with Hydrarg. c. Creta, Acetylsalicylic Acid, Phenacetin, Quinine and its salts, and Sodium Bicarbonate; Suppos. Plumbi c. Opio; Tabl. Plumbi c. Opio; Ung. Gallæ c. Opio; Ung. Gallæ Co.

Registered medical practitioners, dental surgeons and veterinary surgeons are persons authorized to be in possession of Dangerous Drugs, but *only in so far as is necessary* for the practice of their professions. They should know that, before supplying an order or dispensing a prescription, the pharmacist must satisfy himself that the order or prescription and its signature are genuine and from a registered prescriber; the pharmacist endorses the order or prescription with the date of dispensing, records it in his D.D.A. book, copies it in his prescription book, and retains the prescription for two years.

Registered medical practitioners, dental and veterinary surgeons must observe certain regulations when buying, using and supplying Dangerous Drugs for their patients, and the following instructions comply with the requirements of the Acts:

Purchase of Dangerous Drugs.—The prescriber should send or post to the pharmacist a written order bearing his address, his signature, and the statement that the drugs (giving exact quantities) are "for use in his practice." Dental surgeons must add the words "For local dental treatment only," and veterinary surgeons the words "For animal treatment only." Orders, in emergency, by telephone must be confirmed in writing within 24 hours. Alternatively, the prescriber may collect the drugs from the pharmacist and sign the pharmacist's poison book. On receipt of the drugs, the medical practitioner, dental or veterinary surgeon must record the purchase in his Dangerous Drugs' Register for purchases (*see* form below).

Prescribing of Dangerous Drugs.—The prescription must bear (*a*) the name and address of the patient, (*b*) the date, (*c*) the total amount of the drug or the amount of an official preparation (B.P., B.P.C., or N.F.), (*d*) the prescriber's usual signature and, except on National Health and Local Authority forms, his address, and (*e*) either the statement "Not to be repeated" or the dates for repetition. Not more than three supplies are allowed on one prescription, i.e. two repeats; no repeats may be ordered on N.H.A. forms. Dental and veterinary surgeons must endorse their prescriptions as previously stated under "purchase"; veterinary surgeons must substitute for the patient's name and address those of the person to whom the drug is to be delivered.

Administration.—Registered medical practitioners and dental surgeons may administer Dangerous Drugs to patients and veterinary surgeons may administer them to animals without keeping a record of such administration.

Supply.—Medical practitioners may supply Dangerous Drugs for administration to or by a patient, and veterinary surgeons may supply them for administration to animals; but both must keep a record of the supply in the special supply register (*see* form below).

Dental surgeons may not supply these drugs; they are empowered only to give them personally.

FORM OF REGISTER FOR PURCHASES

Date on which received	Name	Address	Amount obtained	Form in which obtained
	of person from whom obtained			

FORM OF REGISTER FOR SUPPLIES

Date of transaction	Name	Address	Authority of person to whom article supplied to be in possession thereof	Amount supplied	Form in which supplied	In case of supply on a prescription, the ingredients of the prescription
	of person to whom supplied					

Separate parts of the Registers must be kept for the following: (1) Cocaine and its preparations, (2) Morphine and its preparations, (3) Diamorphine and its preparations, (4) Medicinal Opium and (5) Extracts or Tinctures of Cannabis Indica.

SAMPLE PRESCRIPTION

For J. Smith Esq.,
10, *Black Street*,
London, *W*.1

℞
Opii pulv. . . . . gr. ½
Bismuth. Carb. . . . gr. xx
Fiat pulv. Mitte tales sex.

Sig.: One powder three times a day before food.
To be repeated on 17th May, 1950, and on 19th May, 1950, only.

15*th May*, 1950.

D. J. RETLAW, M.B., Ch.B.,
20, *White Street*,
London, *W*.1.

Pharmacy and Poisons Act 1933.—This Act provides for the control of the supply of poisons to the public. Under Section 19, a qualified medical practitioner, a dental or veterinary surgeon may supply poisons for the treatment of his patients, subject to the following conditions:—(*a*) the medicine must be distinctly labelled with the name and address of the person by whom it is supplied; and (*b*) a record must be made, on the same day or the day following in a book used regularly, but not exclusively, for this purpose, of the date, the ingredients and the quantities of the medicine supplied.

Fourth Schedule Poisons.—Substances in the Fourth Schedule may be sold by retail only upon a prescription given by a qualified medical practitioner, registered dentist or registered veterinary surgeon. They are: Allyl*iso*propylacetyl urea (Sedormid); Amidopyrine and its salts; Barbituric Acid, Barbiturates, their derivatives and compounds; Dinitro-cresols (Dekrysil), -phenols, -naphthols and -thymols; Sulphonamides and their salts, except in ointments and dressings; Phenylcinchoninic Acid (Cinchophen), Salicyl-cinchoninic Acid, their salts and esters; Sulphonal and Alkyl Sulphonals; and Tridione (Trimethyloxazolidine-dione).

INDEX

AACHEN, 115
Abbreviations, Prescribing, 35
— in Weights and Measures, 12, 13
Abietic Acid, 433
Abortifacients, 377, 578
Abrodil, Per-, 124
Absorption, Intestinal, 489
Acacia, 141
Accessory Food Factors, 187–201
Accommodation, Drugs influencing, 577
A.C.E. Mixture, 281
Acetanilidum, 367
Acetarsol, 108, 258
Aceteugenol, 150
Acetic Acid, 131
Aceto-acetic Acid, 42, 208, 521
Acetomenaphthone, 200
Acetophenetidin, 366
Acetum, 7
Acetylcholine, 324, 325, 326, 327, 328, 329, 330, 332, 334, 554
Acetyl-methylcholine Chloride, 326
Acetylsalicylic Acid, 364
Achlorhydria, 484
Acid, Abietic, 433
— Arabic, 141
— Ascorbic, 193
— Carminic, 140
— Cevitamic, 193
— Chaulmoogric, 439
— Chrysophanic, 167, 170, 171, 172
— Cinnamic, 6, 260, 368, 429
— Cresylic, 424
— Filicic, 181
— Folic, 214, 515
— Gallic, 180
— Geddic, 6
— Glycuronic, 6
— Glycyrrhizinic, 143
— Hippuric, 369
— Hydnocarpic, 439
— Ipecacuanhic, 255
— Isovaleric, 153
— Lysergic, 377
— Nicotinic, 192
— Phenyl-cinchoninic, 376
— Rheotannic, 170
— Ricinoleic, 166, 425
Acidæmia, 44
Acidity, 41, 44, 475
Acidosis, 42, 208, 279, 385, 521, 524
— Chloroform, 42, 279
— Diabetic, 42, 208, 524
Acids, 128–133, 465, 475
— Incompatibles of, 31
— Inorganic, 128
— Organic, 7, 131
Acidum, Aceticum, 131
— — Dilutum, 131
— — Glaciale, 131
— Acetylsalicylicum, 364
— Arseniosum, 95
— Ascorbicum, 193
— Benzoicum, 369
— Boricum, 394
— Carbolicum, 423
— Carbonicum, 138, 541
— Chromicum, 130
— Citricum, 131
— Folicum, 214, 515
— Hydrochloricum, 128
— — Dilutum, 128, 130
— Hydrocyanicum Dilutum, 153
— Hypophosphorosum Dilutum, 128, 130
— Lacticum, 133
— Mandelicum, 373, 568
— Nitricum, 128
— — Dilutum, 130
— Nitro-Hydrochloricum Dilutum, 130
— Oleicum, 386
— Phosphoricum, 128, 130
— — Dilutum, 128
— Pyrogallicum, 427
— Salicylicum, 362
— Tannicum, 177
— Tartaricum, 131
— Trichloraceticum, 132
Acne Vaccines, 443
Aconine, 438
Aconitic Acid, 438
Aconitine, 438
Aconitum, 438
Acridine Dyes, 397
Acriflavine, 397
Acrosyl, 425
ACTH, 217
Actions of Drugs, 11
Adalin, 310
Adams-Stokes Syndrome, 538
Addison's Disease, 216, 526
Adeps, 390
— Benzoinatus, 390
— Lanæ 390
— — Hydrosus, 390
Adermin, 192
Adhesive Plaster, 434
Adjuvant, 34
Administration, Frequency of, 28
— Modes of, 26
— Times of, 28
Adrenalina, 241
Adreno-Corticotropic Hormone, 217, 219
Adsorptive Agents, 186
Aerotherapeutics, 540, 583

Æthanolamina, 440
Æther Anæstheticus, 283
— Solvens, 283
— Vinylicus, 285
Ætheris Nitrosi, Spiritus, 253
Æthisterone, 225, 226
Æthylenum, 288
Æthylis Chloridum, 286
Æthylis Oleas, 385
Ætiology, 458
Agar, 165
Agglutinins, 442
Aglucones, 229, 238, 239
Agranulocytosis, 368, 402, 516
Air, 540, 569
Aix-les-Bains Waters, 115
Albargin, 74
Albaspidin, 181
Albucid, 403
Alcohol, 269
— Benzyl, 422
— Cetosterylicum, 391
— Substances containing, 269
— Tribromœthylicum, 304
Alcoholia Lanæ, 391
Aldehyde Hypnotics, 303
Alimentation, Rectal, 495
Alkalæmia, 42
Alkalinizers of blood, 510
Alkalis, Emulsions, 18
— Incompatibles of, 32
Alkaloids, 6
— Incompatibles of, 32
Alkalosis, 43, 475, 541
Allergy, 30, 456
Allobarbitonum, 314
Allochrysine, 75
Allonal, 368
Allyl Isothiocyanate, 436
Almond Oil, 386
Almonds, Bitter, 154
— — Volatile Oil of, 386
Aloe, 169
— Resin, 169,
Aloinum, 169
Alpha Rays, 590
Alternating Current, 588
Alum Precipitated Toxoid, 449
Alumen, 78
Aluminium Hydroxide, 80, 475, 482, 483
— Salts, 78
— Silicate, 79
Alurate, 315
Alypin, 352
Amblyopia, 71, 98, 100, 108, 183, 320, 355, 553
Ambrine, 389
Amethocain Hydrochloride, 349
Amidone Hydrochloride, 302
Amidophen, 368
Amidopyrina, 368
Aminacrine Hydrochloride, 397
Aminacyl, 411
Aminophylline, 371
Aminoquin, 359
Ammoniæ, Liquor, 49
— — Fortis, 49
Ammonii Acetatis, Liquor, 50
— Bicarbonas, 50
— Chloridum, 50, 52
Ammonium, 49–53
— Ichthosulphonate, 427
— Mandelate, 374
— Nitrate, 53
— Phosphate, 53
Amphetamine, 246
— Sulphate, 246
Amydricaine, 352
Amylase, 162
Amyleni Hydras, 304
Amylis Nitris, 251
Amyl-meta-cresol, 425
Amylobarbitone, 314
Amylocainæ Hydrochloridum, 352
Amylum, 393
Amytal, 314
— Sodium, 314
Anacardone, 266
Anacobin, 215
Anæmia, Aplastic, 515
— Macrocytic, 214, 215, 514,
— Microcytic, 83, 511, 514
— Pernicious, 212, 213, 512, 514
Anæsthesia, Colonic, 304, 314, 315
— General, Phenomena of, 276
— Infiltration, 343, 347, 348, 349
— Intraspinal, 26, 346, 347, 349, 352, 552
— Intravenous, 317, 318, 320, 322, 324
— Regional, 341–352
Anæsthesine, 350
Anæsthetic Mixtures, 281
Anæsthetics, General, 268–289, 553, 555, 558
— — Selection of, 280, 284
— Local, 341–352, 354, 361, 468, 552, 557
— Rectal, 304, 314, 315
Anahæmin, 213
Anal Ointments, 496
Analeptics, 254, 266, 549
Analgesics, 290–303, 362–369, 552, 556
Anaphrodisiacs, 578
Anaphylaxis, 244, 456
Anatoxin, 449
Androgenic Hormones, 223, 228
Anethaine, 349
Anethole, 144, 148, 149
Anethum, 144
Aneurine Hydrochloride, 190
Angina Pectoris, 253, 538
Anhidrotics, 570
Aniline, 428
Anions, 590
Anisi Oleum, 148
Anode, 587
Anodyne Antipyretics, 362–369, 558
— Narcotics, 290–303, 558
Anodynes, Local, 552, 557
Anoxæmia, 136, 519, 541
Antacids, 41–42, 47, 48, 51, 55, 60, 66, 467, 475
— Oral, 467
— Remote, 42, 44, 48, 130, 564
Antazoline, 382
Anthelmintics, 160, 181–186, 495
Anthiomaline, 112
Anthisan, 382
Anthracene, 428
— Purgatives, 167, 492
Anthralin, 429

Anthraquinone Purgatives, 167–172, 492
Antibacterial Sera, 447–455
Antibiotics, 412–422
Anticholera Vaccine, 443
Antidiphtheritic Serum, 450
Antidotes to Arsenic, 82, 115, 383
— to Atropine, 327, 330
— to Bismuth, 115, 383
— to Gold, 75, 383
— to Hydrocyanic Acid, 154
— to Lead, 58, 71
— to Mercury, 115, 383
— to Morphine, 86, 261, 266, 340
— to Phosphorus, 78, 86
— to Snake-bite, 86, 455
— to Strychnine, 127, 280, 306, 316
— to Tubocurarine, 323
Antidysenteric Serum, 454
Anti-Emetics, 479
Antifebrin, 367
Antigen, 442
Anti-histaminics, 382
Antilusin, 324
Antimonii et Potassii Tartras, 109
— et Sodii Tartras, 110
Antimony, 109
Antiphlogistine, 79
Antipyretics, 352–369, 571, 572
Antipyrin, 367
Antiseptics, 394–399, 466, 575, 576
— Aniline Dye, 397–399
— Chlorine, 116
— Dental, 466
— Intestinal, 186, 494, 498
— Metallic, 71–93
— Oral, 466
— Respiratory, 255, 545
— Urinary, 372–374, 565, 568
Antisialagogues, 466
Antispasmodics, Nervous, 153
— Respiratory, 543
Antistin, 382
Antitoxin, Dysenteric, 454
— Gas-Gangrene, 452
— Rabies, 455
— Scarlet Fever, 454
— Therapy, 447–456
Antitoxinum Diphthericum, 450
— Œdematiens, 453
— — Compositum, 453
— Septicum, 453
— Tetanicum, 451
— Welchicum, 452
Antityphoid Vaccine, 444
Antivenom Serum, 455
Aperients, 490
Aphrodisiacs, 578
Apomorphinæ Hydrochloridum, 164
Applicatio, 11
Aqua Aromatica, 7
— Concentrata, 8
— Destillata, 133
— pro Injectione, 133
Aqueous Ointment, 391
Arabin, 6
Arabinose, 6, 142
Arachidic Acid, 385
Arachin, 384, 386
Arachis Oil, 385
Areca Catechu, 332
Arecoline, 332
Argein, 73
Argenti Nitras, 71
— Proteinas Mite, 73
Argento proteinum, 73
Argentum Collosol, 74
Argyria, 73
Argyrol, 74
Arrowroot, 593
Arsacetin, 100
Arseni Trioxidum, 95
Arsenical Poisoning, 97, 107
— — Organic, 105
Arsenium, Salts of, 95
Arsphenamines, 101, 105, 106
Arteries, Drugs affecting, 241–254, 528 533, 538
Arterio-sclerosis, 538
Artificial Sunlight, 590
Ascaridole, 183
Aschheim-Zondek Test, 219
Ascorbic Acid, 193
Asparagin, 143
Aspidinol, 181
Aspirin, 364
Assay, Pharmacological, 109, 188, 195, 196, 206, 210, 226, 227, 229, 238, 247, 446, 451
Asthma, 244, 245, 252, 372, 548
Astringents, Gastric, 479
— Intestinal, 494, 498
— Metallic, 71–93
— Oral, 468
— Vegetable, 177–181
Atebrin, 357
— Musonate, 358
Atoxyl, 100
Atropina, 333
Atropinæ Methonitras, 338
— Sulphas, 333
Atropine, Drugs containing, 332, 333, 339, 341
Aurantiamarin, 160
Aurantii Cortex Recens, 160
— — Siccatus, 160
Aureomycin, 421
— Borate, 421
Auricular Fibrillation, 232, 240, 537
— Flutter, 233, 537
Aurothio-malate, Sodium, 74
Aurula, 11
Autogenous Vaccines, 443
Avertin, 304
Axon Reflex, 573
Azochloramid, 426
Azorubri, Liquor, 140

BACTERIAL VACCINES, 443
Bactericidins, 442
Bacteriolysins, 442
Bagnères-de-Luchon, 115
B.A.L., 383
Balsams, 6
Balsamum Peruvianum, 429
— Tolutanum, 259
Bandages, 580
Barbaloin, 169

Barbitonum, 310
— Sodium, 311
— Solubile, 311
Barbituric Acid Hypnotics, 310–320
Barii Sulphas, 63
Barium, 63–64
— Chloride, 63
— Meals, 64
— Sulphide, 64, 114
Basal Hypnotics, 305, 314, 315, 316, 340
Basic Metabolic Rate, 202, 519
Bassoric Acid, 6, 142
Bath, Waters of, 49
Baths, 582–587
— Air, 514, 583
— Carbonic Acid, 58, 138, 584
— Cold, 582, 583
— Douche, 584
— Electric Light, 589
— — Water, 587
— Medicated, 584
— Nauheim, 58, 138, 584
— Radiant Heat, 589
— Schnee's, 587
— Sea-Water, 584
— Sulphur, 115, 584, 585
— Turkish, 583
— Vapour, 583
— Water, 134, 583
Battiste, 580
Bayer "205," 112
Beating, 581
Beef Tea, 595
Beeswax, 392
Belladonnæ Herba, 332
— Præparata, 332
— Radix, 332
Belladonnine, 332, 333
Bemax, 191
Benadryl, 382
Benzaconine, 438
Benzaldehyde, 155, 386
Benzaminæ Lactas, 351
Benzedrine, 246
— Sulphate, 246
Benzene, 428
— Hexachloride, 431
Benzoic Acid, 369, 429
— — Drugs containing, 6, 260, 368, 429
— Aldehyde, 152
Benzoinum, 368
Benzoresinol, 368
Benzyl Alcohol, 422
— Benzoate, 260, 429, 430
— Cinnamate, 260, 429
Beprochin (*see* Pamaquin)
Berberine Sulphate, 258
Bergonié Treatment, 588
Beri-beri, 190
Bertrich, 585
Beta Rays, 590
Betanaphthol, 427
Beverages, 594
Bile, Drugs influencing, 176, 488, 505
— Ox, 176
— Salts. 176
Biliary Colic, 507
Biniodide of Mercury, 88, 89
B.I.P.P., 66, 125
Bismostab, 65
Bismuth, 64–68
— Emetine Iodide, 257, 258, 500
— Iodoform Paste, 66, 125
— Oxychloride, 64, 65
— Precipitated, 65
Bismuthi Carbonas, 64
— et Sodii Tartras, 65
— Oxychloridum, 64
— Salicylas, 64, 362
— Subgallas, 65
— Subnitras, 66
Bismuthum Præcipitatum, 65
Bitter Stomachics, 158–162, 464
— — Aromatic, 160–162, 465
— — Simple, 158–160
Black Draught, 171
Bladder Sedatives, 565, 568
Blaud's Pill, 80
Bleaching Powder, 116
Blindness, Drugs causing, 71, 98, 100, 108, 183, 320, 355, 553
— Night, 189
Blisters, 573
Blood, 508–517
— Alkalinizers of, 510
— Pharmacology, 508–513
— Pressure, Substances influencing, 241–254, 531
— Therapeutics, 513–517
— Transfusion, 509
Blue Pill, 86
— Vitriol, 77
Bluestone, 77
Body Heat, 569–572
— — Drugs influencing, 352–369, 569
— — Pharmacology, 569
— — Therapeutics, 571
Borax, 395
— Emulsions, 18
Bordeaux B, 140
Boric Acid, 394
— Gauze, Lint, Wool, 579
Borneol, 149, 151, 152
Bornyl Acetate, 152
— Isovalerate, 153
Borocaine, 352
Bottles, Sizes of, 17
Bougies, 11, 23
Brandy, 269
Bread, 593
Breath, Fetid, 470
Bright's Disease, 566
Brilliant Green, 399
British Pharmaceutical Codex, 3
— Antilewisite, 383
— Pharmacopœia, 2
Bromethol, 304
Bromides, 125–128
Bromine, 125
Bromism, 127
Bromural, 310
Bromvaletonum, 310
Bronchioles, Drugs acting on, 255, 542, 546
Bronchitis, 545
Broom, 321
Brucine, 263, 266
Buchu, 3
Burnol, 389
Burns, Treatment of, 178, 389

Butacainæ, 348
Butesin, 350
Butobarbitone, 315
Butolan, 185
Butter, 594
Butyl Aminobenzoate, 350
Butylchloral Hydrate, 307
Butyn, 348
Butyric Acid, 518, 521
Buxton, 49, 523

CACAO BUTTER, 393
Cachet, 11, 23
Cade, Oil of, 428
Cadinene, 428
Caffeina. 260
— et Sodii Benzoas, 261
Caffeotannic Acid, 263
Cajuput Oil, 152
Calabar Bean, 326
Calamine, 76
Calciferol, 195
Calcii Carbonas, 53
— Chloridum, 53
— — Hydratum, 54
— Gluconas, 54
— Hydroxidum, 53
— Hypophosphis, 95
— Lactas, 54
— Phosphas, 54
Calcium, 53–59
— Gluconate, 54
— Lævulinate, 58
— Mandelate, 373
— Metabolism, 205
— Sodium Lactate, 58
Calculus, Renal, 522, 568
Calomel, 87, 89, 90, 93
— Cream, 92
Caloric Requirements, 591
Calumba, 158
Calves' Foot Jelly, 143
Calx Chlorinata, 115
— Sodica, 58
Camphene, 150, 151, 153
Camphor, Ammoniated Liniment of, 50 435
Camphora, 434
Camphorated Oil, 435
Camphorol, 436
Campolon, 213
Cannabinol, 303
Cannabinone, 303
Cannabis Indica, 303
Capacity, Measures, 13
Capillaries, Drugs influencing, 529, 532
Caprokol, 373
Capsaicin, 437
Capsicum, 437
— Wool, 438, 579
Capsules, 11, 23
Caraway, 148
Carbachol, 325
Carbamide, 372
Carbaminoyl-choline, 325
Carbarsone, 108, 258
Carbasus Absorben, 579
Carbo, 187
Carbohydrates in Diet, 593
Carbolic Acid, 423
Carbolic Gauze, Tow, 580
Carbon Dioxide, 138, 541
— — Baths, 58, 138, 584
— — Snow, 138
Carbonei Tetrachloridum, 184
Carbromal, 310
Carcinoma Prostatic, Œstrogen Treatment, 223
Cardamomum, 149
Cardiac Failure, 233, 534
— Tonics, 228–241, 530, 534–538
Cardiazol, 267
Cardio-vascular Diuretics, 563
Carene, 432
Cargile Membrane, 580
Carminatives, 144–155, 477, 494, 502
Carmine, 140
Carotene, 188, 189
Carrel-Dakin Irrigation, 117
Carron Oil, 54, 387
Carum, 148
Carvene, 148
Carvone, 148
Caryophyllene, 150
Caryophyllin, 150
Caryophyllum, 149
Cascara Sagrada, 168
Casein Hydrolysate, 201, 488
Castile Soap, 387
Castor Oil, 166
Cataplasma, 8, 79
Catechin, 179
Catechu, 179
— Red, 179
— Tannic Acid, 179
Cathartics, 492
Cathode, 587, 590
Caustic, Lunar, 71
— Potash, 46
Caustics, 41, 47, 54, 72, 76, 77, 85, 96, 129, 132, 133, 138, 362, 423, 468
— Oral, 468
Cayenne Pepper, 438
Cellulose Wadding, 579
Cephaëline, 255
Cera Alba, 393
— Emulsificans, 392
— Flava, 392
Cerebral Depressants, 268–320, 553–555
— Stimulants, 260–268, 552–554
Cerolein, 392
Cerotic Acid, 392
Cetaceum, 391
Cetavlon, 422
Cetin, 391
Cetostearyl Alcohol, 391
Cetrimide, 422
Cevitamic Acid, 193
Chalk, 53
Challes Waters, 115
Chalybeate Waters, 85, 586
Charcoal, 187
Charta, 11
Chasmantherin, 158
Chaulmoogra Oil, 440
Chaulmoogric Acid, 439
Chavicol, 148
Cheltenham, 43, 62
Chemical Food, 81

Chemotherapy, 1
Chenopodium Oil, 183
Cheyne-Stokes Respiration, 137
Chiniafonum, 361
Chloralamide, 308
Chloralformamidum, 308
Chloral Hydras, 305
— — and Camphor, 305, 435
Chloramina, 116
Chloramphenical, 421
Chlorbutol, 307
Chloretone, 307
Chlorinated Lime, 115
— Soda, 116
— Xylenol, 425
Chlorine, 115
— Antiseptics, 115
— Ions, 590
Chloroazodin, 426
Chlorocresol, 425
Chlorodyne, 274, 275, 294
Chloroformum, 274
— Administration of, 280
— Delayed Poisoning, 279
Chloromycetin, 421
Chloroquine Diphosphate, 359
Chlorosis, 511
Chloroxylenol, 425
Cholagogues, 176, 488, 505
Cholera, Treatment of, 499
— Vaccines, 443
Cholesterol, 196, 390
Choline, 238, 303
Chorea, 560
Chromatopsia, 183
Chromic Acid, 130
Chromii Trioxidum, 130
Chrysarobinum, 429
Chrysophanic Acid, 167, 170, 171, 172
Cibalgin, 368
Cignolin, 429
Cinchocaine Hydrochloride, 348
Cinchona (*see* Quinine)
Cinchonism, 355
Cinchophenum, 374, 376
Cineole, 147, 149, 151, 152, 434
Cinnamic Acid, 6, 260, 368, 429
— Aldehyde, 151
Cinnamomum, 151
Circulation, 527–539
— Drugs acting on, 228–254, 529
— Pharmacology, 527–533
— Therapeutics, 533–539
Circulatory Stimulants, 228–254, 271, 529–539
Cirrhosis, Hepatic, 506
Citral, 162
Citric Acid, 131, 162
Citronellal, 162
Citrullol, 174
Clapping, 581
Cloves, 145, 149, 150
Clyster, 11
Coagulability, Drugs accelerating, 510
Coagulose, 455
Coal Tar, 428
Cocaina, 342
Cocainæ Hydrochloridum, 342
Cocaine, Prescribing Restrictions, 595
Cocainism, 345
Cocculin, 268
Coccus, 140
Cochineal, 140
Codamine, 290
Codeina, 290, 292, 300
Codeinæ Phosphas, 300
Codex, British Pharmaceutical, 3
Cod-liver Oil, 196, 198
Coffee, 261
Colchici Cormus, 374
— Semen, 375
Colchicine, 375
Collagen, 194
Collargol, 73
Collodium, 8
— Flexile, 393
Colloidal Gel, 6
— Silver, 73
— Sol, 6
Collunarium, 11
Collutorium, 11
Collyrium, 11
Colocynthin, 174
Colocynthine, 174
Colocynthis, 174
Colophonium, 433
Colouring Agents, 140
Columbamine, 158
Columbin, 158
Coma, Diabetic, 43, 156, 209, 524
Combination of Drugs, 33
Comminution, 14
Composition of Drugs, 5
Compounding of Prescriptions, 14
Compral, 368
Condenser Discharges, 587
Coniferyl Alcohol, 368
Coniine, 321
Consciousness, 555, 560
Constipation, Treatment of, 500
Contrexéville Waters, 49, 585, 586
Convulsions, Treatment of, 559
Co-ordination Exercises, 582
Copaiba, 374
Copper Ions, 590
— Salts, 77
Coramine, 266
Coriandrol, 149
Coriandrum, 148
Coronary Circulation, 531
Corpus Luteum Hormone, 219, 224, 225
Corrective, 33, 34,
Corrosive Sublimate, 87
Corticosterone, 216
Cortisone, 216
Cotton Seed Oil, 386
Cotton Wool, 579
Cough, Treatment of, 255, 543, 544, 545
Counter-irritants, 432–440, 573–576
Cream, 594
— Calomel, 92
— of Tartar, 46
Cremor, 8
Creolin, 425
Creosol, 426, 428
Creosotum, 426
Cresol, 424, 428
— Amyl-meta-, 425
Cresylic Acid, 424
Creta, 53

Cretinism, 203, 526
Crotin, 176
Croton Oil, 175
— Resin, 175
Crymotherapy, 138
Cryptopine, 290, 300
Cryptoxanthine, 188
Crystal Violet, 186, 398
Cubebs, Oil of, 374
Cumulation, 30
Cupri Sulphas, 77
Curarine, 321
Curd Soap, 387
Cyclobarbitone, 316
Cycloplegia, 334
Cyclopropane, 288
Cyllin, 425
Cymarin, 238
Cytamen, 215

DAGGA, 303
Dakin's Solution, 116
Dangerous Drugs Acts, 595
— — Administration, 597
— — Prescribing of, 596
— — Purchase of, 596
— — Supply of, 597
Datura Folia, 341
— Semina, 341
D.D.T., 431
Decamethonium Iodide, 323
Decantation, 15
Decicain, 349
Decoction, 15
Decoloration, 15
Defatting, 15
Deficiency Diseases, 187–228, 250, 525
Demerol, 301
Demulcents, 141–144, 466
Dental Diseases, 470
Dentifrices, 41, 55, 60
Deodorants, 85, 116, 396
Deoxycortone Acetate, 215
Depilatories, 64, 71, 114
Depressants, Cerebral, 553, 554, 555
— Muscular, 321–324
— Nervous Motor, 554
— — Sensory, 552
Dermatol, 65
Derris Præparata, 430
Desiccation, 14
Desoxycorticosterone Acetate, 217
Dettol, 425
Devitalizing Agents, 96
Dextrose, 156
— Monohydrate, 157
Dextrosum Hydratum, 157
D.F.P., 330
Diabetes Insipidus, 249, 567
— Mellitus, 208, 523
— — Diet in, 208, 523, 593
Diabetogenic Hormone, 219
Diacetylmorphine Hydrochloride, 301
Diagnostic dyes, 440
Dial, 314
Diamino - dihydroxy - arseno - benzene, 98, 100
Diamorphinæ Hydrochloridum, 301
Diamorphine, Prescribing Restrictions, 595
Diaphoretics, 331, 352–369, 570, 571
Diarrhœa, Diet in, 497
— Infective Infantile, 500
— Lienteric, 500
— Nervous, 500
— Treatment of, 496–498
Diasone, 410
Diastase, 198
Diathermy, 588
Dibenamine, 254, 539
Dick Test (Scarlet Fever), 454
Dicophane, 431
Dicoumarol, 211
Dienœstrol, 221
Diet, Antiketogenic, 208
— Diabetic, 208, 523, 593
— Fluid, 595
— Full, 595
— Invalid, 591–595
— Lenhartz, 484, 593
— Light, 595
— Meulengracht, 484
Diethyl Ether, 283
Diethylstilbœstrol, 221
Digestion, 15
Digestive Ferments, 162, 163
— System, 463–503
— — Drugs acting on, 140–187
Digitalin, Nativelle's, 237
Digitalis Folium, 228
— Lanata, 237
— Præparata, 229
Digitoxigenin, 229
Digitoxin, 239, 236, 237
Digitoxinum, 236
Digitoxose, 229
Digoxinum, 237
Dihydrostreptomycin Sulphate, 421
Di-Insulin, 209
Dill, 147
— Fruit, 144
Dimercaprol, 115, 383
Dimethylphthalate, 431
Dinitro-Cellulose, 393
Diodoni Injectio, 124
Dioxyanthranol, 429
Diphenanum, 185
Diphenhydramine, 382
Diphtheria Antitoxin, 450
— Prophylactic, 449
Disease, Dosage in, 30
Disephonine, 302
Disinfectants, 394–431
Dispensing, 14
Distaquaine, 416
Distillation, 15
— Fractional, 15
Dithranol, 429
Diuretics, 369–372, 563
— Mercurial, 93–94
— Saline, 40, 48, 563
Diuretin, 370
Dolantin, 301
Domestic Measures, 14, 32
Dormigene, 310
Doryl, 325
Dosage, Conditions modifying, 27–31
— for Children, 28

Douche, 584
— Aix-, 584
— Vichy, 584
Dover's Powder, 256, 257, 291, 298
Drachm Symbol, 12–13
Drastic Purgatives, 173–176, 492
Draughts, 11, 19
Dressing, First Field, 579
— Tillmann's, 579
Dressings, Medicated, 579–580
— Waterproof, 580
Drill, Swedish, 582
Droitwich Waters, 39
Drops, 11, 14, 17, 27
Dropsy, 536, 566
Drug Habit, 30, 274, 299, 301, 302, 306, 309, 311, 345
Drugs, Actions of, 11
— Acts, Dangerous, 595
— Administration of, 26
— Calculating Doses of, 27
— Characters of, 4
— Combination of, 33
— Composition of, 5
— Cumulation of, 30
— Impurities of, 5
— Incompatibilities of, 31
— Preparations of, 7
— Sources and Natures of, 4
— Tolerance of, 30
— Weighing and Measuring of, 16
Duodenal Ulcer, 483
Duodenum, 487–503
— Pharmacology, 487–496
— Therapeutics, 496–503
Duomycin, 421
Durocaine, 348
Dusting Powders, 54, 60, 66, 76, 79, 108, 350, 394, 395
— — for Pills, 21
Dyes, diagnostic, 440
Dyschezia, 501
Dysentery, Amœbic, 108, 257, 500
— Bacillary, 454, 499
— Vaccine, 444
Dyspepsia, 480–482
— Atonic, 480
— Hypertonic, 42, 481
Dyspnœa, 546

EAR MEDICATION, 11, 27
Ecbolics, 377
Ecgonine, 595
Effleurage, 580
Egg Emulsions, 19
Elæoptene, 6, 144
Elaterin, 174
Electric Light Baths, 589
Electrical Treatment, 587–590
Electricity, Alternating, 588
— Faradic, 588
— Galvanic, 587
— Sinusoidal, 588
Electro-cardiogram, 527
Electrolysis, 588, 590
Electro-Therapeutics, 587–590
Elixir, 8
Elutriation, 15
Embrocation, 9
Emetics, 163–165, 477
— Central, 163, 478
— Metallic, 41, 52, 77, 78, 79, 110
— Reflex, 163, 256, 477
— Use of, 486
Emetine, 255, 257
— Bismuth Iodide, 257, 258, 500
— Hydrochloride, 257, 500
— Periodide, 258
Emmenagogues, 377
Emodin, 167, 168, 169, 170, 171
Emollients, 384–394
Empirical Treatment, 461
Emplastra, Dispensing of, 25
Emulsification of Oils, 18
Emulsio, 8
— Chloroformi, 274
— Menthæ Piperitæ, 147
Emulsions, Compounding of, 18
Endocarditis, 538
Enemata, 11, 27, 388, 394, 495, 502
Enteric Coatings, 22
Enzymes, 162–163
Epanutin, 313
Ephedrina, 244
Ephedrinæ Hydrochloridum, 245
Epilepsy, 127, 312, 313, 560
Epinephrin, 241
Epispastics, 573
Epsom Salts, 60
Equivalents, Imperial and Metric, 12–13, 36
Ergobasine, 378
Ergocornine, 377
Ergocrystine, 377
Ergokryptine, 377
Ergometrinæ Maleas, 378, 379
Ergometrine, 377, 378, 379
Ergonovine Maleate, 378
Ergosterol, 195
Ergota, 377
Ergotamine, 377, 378
— Tartrate, 378, 380
Ergotherapy, 588
Ergotism, 380
Ergotoxine, 377, 378, 380
Eriodictyol, 195
Erion (*see* Mepacrine)
Erythræmia, 515
Escharotics (*see* Caustics)
Eserine, 326
Essential Oils, 6, 144
Estigyn, 224
Ethanolamine, 440
Ether, 287
— Vinyl, 285
Ethereal Oils, 6, 144
— Soap, 283, 387
Ethinyl Œstradiol, 222, 224
Ethisterone, 225, 226
Ethocaine, 346
— Borate, 352
Ethyl Carbamate, 309
— Chaulmoograte, 440
— Chloride, 286
— Oleate, 385
— Pyrophosphate, 329
Ethylene, 288
Eucaine, Beta, 351
Eucalyptol, 147, 151, 152 434

Eucalyptus Oil, 434
Euflavine, 397
— Lint, 579
Eugenol, 150, 151
Eulissen, 323
Eumydrin, 338
Euphyllin, 371
Euquinine, 354
Eusol, 117
Evaporation, 15
Evipan, 317
— Sodium, 317
Examen, 213
Excipients for Pills, 21
Exercises, Graduated, 582
— Resistance, 582
— Respiratory, 545, 582
Expectorants, 254–260, 542, 545
Extractives, 594
External Remedies, 384–399, 573–576
Extract of Malt, 198
Extracts, 8
— Standardized, 8
Extractum Compositum, 8
— Liquidum, 8
— Siccum, 8
Eye, Medication of, 27
— Substances acting on, 576–578
— Wash, 11 ,19

FARADISM, 588
Farinas, 593
Fasting Treatment, 592
Fats in Diet, 594
Fatty Degeneration, 97, 111, 184, 279, 376, 506
Fellis Bovini, Extractum, 176
Felt Dressings, 580
Fenchone, 149
Fennel, 149
Ferments, 162–163
Ferri Carbonas Saccharatus, 80
— et Ammonii Citras, 81
— Hydroxidum, 82
— Perchloridi, Liquor, 81
— Phosphatis Compositus, Syrupus, 81
— Sulphas, 80
— — Exsiccatus, 80
Ferric Hydroxide, 82
Ferrivenin, 85, 511
Ferrum, 80
Fever, 571
Fibrillation, Auricular, 232, 240, 537
Fibrin Foam, Human, 457
Fibrinogen, Human, 457
Figs, Syrup of, 172
Filicic Acid, 181
Filicin, 181
Filicitannic Acid, 181
Filix-Mas, 181
Filmarone, 181
Filtration, 15
Finsen-Reyn lamp, 590
Fish Diet, 592
Flatulence, Treatment of, 502
Flavine, 397
Flavouring Agents, 144–155
Flaxedil, 323
Flitwick Waters, 85
Fluoresceinum Sodium, 440
Fluorophosphonates, 330
Flutter, Auricular, 233
Fly Agaric, 332
Fœniculum, 149
Folic Acid, 214, 515
— — Antagonists, 218
Foods, 463, 591–595
Formalin, 422
Formol Toxoid, 449
Formulary, National, 3
Fouadin, 111
Fowler's Solution, 95
French Chalk, 21, 60
Friar's Balsam, 368
Friction, 580
Fructose, 157
Fruit in Diet, 490, 501, 593
F.S.H. Hormone, 227
Furfural, 150
Fusion, 15

GALACTAGOGUE, 219, 248
Galactose, 6, 142, 166
Galenical Pharmacy, 14
Gallamine, 323
Gall Stones, Treatment of, 507
Galvanism, 587
Gambier-Fluorescein, 179
Game in Diet, 592
Gamgee Tissue, 579
Gammexane, 431
Gamma Rays, 590
Ganglia, Drugs acting on, 320–321, 555
Gardan, 368
Gardenal, 311
Gargarisma, 11
Gas-Gangrene Antitoxins, 452
Gaster Siccata, 215
Gastrexo, 215
Gastric Hæmostatics, 479, 483
— Sedatives, 474, 476
— Stimulants, 158–162
— Ulcer, 483
Gastritis, Acute, 484
— Chronic, 481
Gauze, Bleached, 579
Gelatinum, 9, 142
Gelose, 166
Gelsemii Radix, 321
Gelsemine, 321
Gelseminine, 321
General Therapeutics, 458–598
Generative Organs, Drugs acting on, 218–228, 250, 578
Gentiamarin, 160
Gentian Violet, 186, 398
Gentiana, 160
Gentiin, 160
Geraniol, 149, 152
Germanin, 112
Gin, 269
Ginger, 151
Gingerol, 151
Gitalin, 229
Gitoxigenin, 229
Gitoxin, 229
Glauber's Salt, 38
Globin Insulin, 209

Glucose Injections, 156, 208, 280, 521, 524
Glucosum Liquidum, 156
Glycerina, 9, 389
Glycerinum, 9, 389
Glycerol, 389
Glycerophosphates, 95
Glycocholate, Sodium, 176
Glycogelatinum, 142
Glycolysis, Drugs influencing, 505
Glycosides, 6, 229
Glycosuria, 207, 243, 523
— Alimentary, 522–523
— Renal, 523, 567
Glycyrrhiza, 143
Glycyrrhizin, 143
Gnoscopine, 290
Goitre, 526
Gold, Antidotes to, 75
— Salts, 74–75
Gonadotrophic Hormones, 218–228
Gonadotrophicum Chorionicum, 226
— Sericum, 226
Gossypium Absorbens, 579
Goulard's Extract, 68
— Lotion, 68
Gout, 375, 376, 521, 525, 567
— Drugs influencing, 374–376
Graduated Exercises, 582
Granulation, 15
Gregory's Powder, 170
Grey Powder, 86
Guaiacol, 426, 428
Guarana, 261
Gum, 6
— Acacia, 6, 141
— Emulsions, 19
— Resins, 6
— Saline Injection, 40, 141
— Tragacanth, 6, 141
Gunjah, 303
Gustatory Stimulants, 464
Guttæ, 11, 14, 17, 27
Gutta-percha Tissue, 580
Guy's Pill, 93
Gynocardia (Hydnocarpus) Oil, 439

HABITS, DRUG, 30, 274, 299, 301, 302, 306, 309, 311, 345
Hacking, 581
Hæmatemesis, 483
Hæmatinics, 78, 84, 86, 96, 212, 213, 511, 514
Hæmatoporphyrinuria, 309, 513
Hæmoglobin, 508
— Drugs altering, 513
Hæmoplastin, 455
Hæmostatic Sera, 455
Hæmostatics, 510, 516, 532
— Gastric, 479, 483
Hæmostyl, 455
Halazone, 116
Halibut-liver Oil, 188
Halogen Disinfectants, 115, 467
— Hypnotics, 304–308
Hamamelis, 180
Harrogate Waters, 85, 115, 523
Hartmann's Solution, 37, 43, 133
Hashish, 303
Haustus, 11
Hay-fever Vaccine, 456
Health, 458
Heart, 527–539
— Drugs acting on, 228–241, 529–533
— Pharmacology, 529
— Therapeutics, 533
Heat Centres, 569, 571
— of Body, 569–572
— Treatment by, 583, 588, 589
Heat Regulation, Drugs acting on, 353–369, 569–572
Hebaral Sodium, 317
Heliotherapy, 589
Hemlock, 320
Henbane Leaves, 339
Hepar Proteolysatum, 214
Heparin, 210, 517
Hepastab, 213
Hepatex, 213
Hepatic Stimulants, 505
Hepatis, Extractum Liquidum, 212
Hepatitis, 506
Hepol, 213
Heptalgin, 302
Heroin, 301
Hesperidin, 160, 161, 195
Hexamethonium Bromide, 324
— Iodide, 324
Hexamethylene Tetramine, 372
Hexamina, 372
Hexobarbitone, 317
— Sodium, 317
— Soluble, 317
Hexœstrol, 221
Hexyl-Resorcinol, 186, 373
Hiccough, 51, 486
High-Frequency Currents, 588
Hippoglossi, Oleum, 188
Hippuric Acid, 369
Histaminæ Phosphas Acidus, 380
Histamine, 377, 381
— Triple Response, 381
Hog's Stomach, Desiccated, 215
Holocaine, 352
Homatropinæ Hydrobromidum, 338
Honey, 9, 143
Hormones, 201–228, 241, 246
Horse Serum, Normal, 455
Hunyadi Janos Waters, 62
Hutchinson's Teeth, 92
Hyalase, 457
Hyaluronidase, 457
Hydnocarpic Acid, 439
Hydnocarpus Oil, 439
Hydragogue Purgatives, 173, 492
Hydrargyri Oxidum Flavum, 87
— Oxycyanidum, 87, 88, 92
— Perchloridum, 87, 88, 89
— Subchloridum, 87, 88, 89
Hydrargyrism, 91
Hydrargyrum, 86
— Ammoniatum, 87, 89
— Oleatum, 88, 89
Hydrochloric Acid, 128
Hydrocotarnine, 290, 300
Hydrocyanic Acid, 154, 155
— — Dilute, 153
Hydrogen Oleate, 386
— Peroxide, 396, 466

Hydroquinone, 424
Hydrous Ointment, 391
Hygiene, 460
Hyoscinæ Hydrobromidum, 339
Hyoscine, Drugs containing, 332, 333, 339, 341
Hyoscine-Morphine Narcosis, 298, 340
Hyoscyamine, Drugs containing, 332, 333, 334, 339, 341
Hyoscyamus, 339
Hyperchlorhydria, 42, 55, 61, 66, 335, 384, 475, 481
Hyperthyroidism, 202
Hypertonic Saline, 39, 40, 41
Hypnotics, 127, 303–320, 556–561
Hypochlorhydria, 130, 475, 480
Hypodermic Injection, 9, 26
Hypoglycæmia, 156, 207, 521, 523
Hypophosphites, 95
Hypophosphorous Acid, 128
Hyposulphite, Sodium, 115
Hypotonic Saline, 40

ICHTHAMMOL, 427
Ichthyol, 427
Idiosyncrasy, 30
Immunity, 441, 447, 513
— Active, 441, 447
— Passive, 441, 447
Imperial Drink, 47
— System, 12–13
Impurities of Drugs, 5
Incompatibility, 31–32
— Chemical, 31
— Pharmacological, 31
— Physical, 31
Indian Hemp, 303
Infantile Diarrhœa, 500
Infiltration, 26, 347, 348, 349
Inflammatory disorders, 470
Infra-red Rays, 589
Infusions, 9, 15
Infusum Concentratum, 9
— Recens, 9
Inhalations, 11, 26
Injectio, 9
Injection, Rectal, 11, 27
— Urethral, 27
Injections, Hypodermic, 9, 26
— Interstitial, 26,
— Intradermal, 381
— Intramuscular, 9, 26
— Intraperitoneal, 26
— Intrathecal, 26, 347, 349, 451, 552
— Intravenous, 9, 26
— Parenteral, 26
— Subcutaneous, 9, 26, 35
Inorganic Acids, 128–131
— Materia Medica, 37–139
Insecticides, 430, 431
Insomnia, Drugs influencing, 127, 290–320, 556, 560
Insufflatio, 11
Insulin, 205–210, 520, 523–525
— Action, Retarded, 209
— Globin, 209, 521, 524
— Zinc Protamine, 206, 209, 210, 521, 524
Internal Secretions, 201–228, 241, 247
Intestinal Antiseptics, 186, 494, 498
— Astringents, 494, 498
— Carminatives, 494, 498
— Protectives, 493
— Sedatives, 187, 493
— Stimulants, 165–176, 249, 489, 493
Intestine, 487–503
— Absorption from, 489
— Drugs influencing, 489–496
— Neuromuscular Stimulants, 493
— Pharmacology, 487–496
— Therapeutics, 496–503
— Transmission in, 489
Intracranial Tension, 559
Intramuscular Injection, 9
Intravenous Injection, 9, 26
Inunction of Mercury, 89
Iodatol, 124
Iodi, Liquores, 118
Iodine, 118
— Compounds in Radiography, 122
— Ions, 590
— Liquores, 118
— Lugol's, 118, 121
— Stains, Removal of, 119
— Tinctures, 118
Iodisatum, Oleum, 124
Iodism, 120
Iodoform Bismuth Paste, 66, 125
Iodoformum, 124
Iodophthalein, 122
Iodoxyl, 123
Iodum, 118
Ionic Medication, 590
Iontophoresis, 590
Ipecacuanha, 255
Ipecacuanhic Acid, 255
Ipomœa, 173
— Resina, 173
Ipral, 315
Iron, Absorption of, 82
— Incompatibles of, 81
— Oxide, Saccharated, 85, 511
— Salts of, 80–81
Isomyn, 246
Isoprenaline, 244
Isopropyl-*nor*-Adrenaline, 244
Isoquinoline Alkaloids, 290, 299
Izal, 425

JABORANDI (*see* Pilocarpinæ Nitras)
Jaconet, 580
Jalap, 173
Jateorhizine, 158
Jaundice, Treatment of, 45, 506
Jeyes' Fluid, 425
Juniper Tar Oil, 428

KÆMPFEROL, 171
Kaladana, 174
Kaolinum Leve, 79
— Ponderosum, 79
Kapilion, 199
Karlsbad, 43, 49
Kathode, 587, 590
Kations, 590
Kemethal, 320
Kephalin, 456

Keratin Coating for Pills, 22
Kerocaine, 346
Kerol, 425
Ketogenic Diet, 373
— Hormone, 219
Ketone Hypnotics, 303
Ketosis, 42, 44, 156, 208, 209, 283, 385
Kharsulphan, 99
Kidneys, 562–568
— Drugs acting on, 369–376, 562–568
— Pharmacology, 562–565
— Therapeutics, 565–568
Kino, 180
— Tannic Acid, 180
Kissingen, 49
Kneading, 581
Kombic Acid, 238
Krameria, 179
— -tannic Acid, 179
— -red, 179
Krysolgan, 75

LACHESINÆ CHLORIDUM, 338
Lachrymal Gland, Drugs influencing, 577
Lactation, Dosage during, 28
Lactic Acid, 133
Lactobacillus casei factor, 214
Lactoflavin, 191
Lactosum, 155
Lævulose, 157
— Tolerance, 157
Lævulosum, 157
Lamellæ, 9
Lanette Wax, 391
Lanolin, 390
Lard, 390
Laudanine, 290, 299
Laudanosine, 290
Laudanum, 291
Laughing Gas, 286
Lauryl Thiocyanate, 430
Lavender Oil, 152
Laxative, 166, 490
Lead, 68–71
— Poisoning, 70
— Salts of, 68
Leamington Waters, 43
Lecithin, 95
Lemon Juice, 132, 162
— Peel, 161
Lenhartz Diet, 484, 593
Leptazol, 267
Lethane Oil, 430
Leukæmia, 515
Levico Waters, 85
Levigation, 14
L.H. Hormone, 218, 226
Light Therapy, 589
Lignocaine, 351
Lime, Slaked, 53
— Water, 53, 54
Limonene, 144, 147, 149, 152, 161, 162
Limonis Cortex Recens, 161
— — Siccatus, 161
— Linalol, 149, 152
Linalyl Acetate, 152
Linctus, 11
Liniments, 9, 19
Linoleic Acid, 385, 386, 387
Linolein, 384
Linolenic Acid, 387
Linseed, 387
Linseed Tea, 387
Lint, Absorbent, 579
Linum Contusum, 387
Lipase, 162
Lipiodol, 124
Liquor, 9
— Ammoniæ, 49
— Azorubri, 140
— Calcis, 53
— — Saccharatus, 55
— Cresolis Saponatus, 424
— Formaldehydi, 422
— Hydrogenii Peroxidi, 396
— Iodi, 118
— Pentosi Nucleotidi, 217
— Ruber, 140
— Sodii Hydroxidi, 37
Liquorice, 143
— powder, compound, 114, 143
Litharge, 68
Lithii Carbonas, 49
— Citras, 49
Lithium Antimony Thiomalate, 112
Liver, 504–507
— Extracts, 213
— Necrosis, 98, 107, 111, 184, 279, 376, 506
— Pharmacology, 504–506
— Therapeutics, 506–507
Llandrindod, 115
Llanwrtyd, 115
Lobeline Hydrochloride, 268
Loganin, 263
Lonchocarpus, 430
Lopion, 75
Lotion, 9, 19
— Red, 76
Lozenge, 10
Lugol's Iodine, 118, 121, 526
Lumbar Anæsthesia, 26, 347, 348, 349 552
Luminal, 311
Lycopodium, 21
Lynoral, 224
Lysergic Acid, 377
Lysol, 424

MACERATION, 8, 10, 15
Magnesia Levis, 59
— Ponderosa, 59
Magnesii Bicarbonatis, Liquor, 59
— Carbonas Levis, 59
— — Ponderosus, 59
— Hydroxidi, Mistura, 59
— Oxidum Leve, 59
— — Ponderosum, 59
— Sulphas, 60
— Trisilicas, 59, 61
Magnesium, 59–63
— Ions, 590
— Peroxide, 60, 396
— Phosphate, Tribasic, 61
— Silicate, 60
— Trisilicate, 59, 61, 475, 482, 488
Malaria, Quinine in, 356
Male Fern, 181

Male Hormones, 227–228
Malt Extract, 198
Maltose, 198
M. and B. " 693," 408, " 760," 404
Mandecal, 374
Mandelic Acid, 373, 568
Mandelonitrile, 154
Manganese Salts, 85
Mantoux Test, 446
Mapharsen, 99
Mapharside, 99
Maphenide, 403
Marfanil, 403
Marienbad Waters, 43, 523
Marihuana, 303
Marmite, 191
Massage, 580–592
— Douche, 584
Maté, 261
Materia Medica, Definition of, 1
— — Inorganic, 37–139
— — Vegetable and Animal, 140-457
Measles Convalescent Serum, 455
Measures, Domestic, 14, 32
— Equivalent, 13, 36
— Imperial, 12, 36
— Metric, 12, 36
Measuring of Drugs, 16
Meat in Diet, 592
— Extract, 594
Mecholin, 326
Mecholyl, 326
Meconic Acid, 290
Meconin, 290
Medinal, 311
Mel Depuratum, 143
Melissyl Alcohol, 392
— Palmitate, 392
— Stearate, 392
Menadione, 199
Menaphthone, 199
Menstruation, Dosage during, 28
Menthæ Piperitæ, Oleum, 147
Menthol, 147, 436
Menthone, 147
Menthyl Acetate, 147
Mepacrine Hydrochloride, 357
— Methanesulphonate, 358
Mephenesin, 324
Meprochol, 331
Mepyramine Maleate, 382
Mercurgan, 93
Mercurial Creams, 86, 87, 92
— Teeth, 92
Mercuric Potassium Iodide, 88
Mercurin, 94
Mercurochromum, 94
Mercury, 86
— Biniodide of, 88, 89
— Oil, 88
— Poisoning by, 91
— Salts of, 86–88, 93-94
Mersalylum, 93
Mesulphenum, 115
Metabolism, 518–526
— Drugs influencing, 201-228, 519-522
— Pharmacology, 518-522
— Therapeutics, 522-526
Meteorism, 502
Methacholine, 326
Methæmoglobin, 47, 253, 367, 368, 513
Methedrine, 247
Methenamine, 372
Methionine, 200
Methyl Amyl Ketone, 150
— Chavicol, 148
— Phenobarbitonum, 313
— Salicylas, 366
— Testosterone, 227
— Thiouracil, 203
— Violet, 398
Methylamphetamine, 246
— Hydrochloridum, 247
Methylated Spirit, 269
Methylene Blue, 441
Methylsulphonal, 309
Methylthioninæ Chloridum, 441
Methylthiouracil, 203
Metrazol, 267
Metric Prescribing, 35
— System, 12, 36
Meulengracht Diet, 484
Meyer-Overton Theory, 277
Miadone, 302
Migraine, 558
Milk Diet, 594
— Sour, 133
— Sugar, 155
Mindererus' Spirit, 50
Mineral Waters, 584
Mistura, 9
Mistura Alba, 62, 491
Mitigal, 115
Mixtures, Compounding, 17
Monsol, 425
Morphinæ Hydrochloridum, 291
— Sulphas, 292
Morphine, 290
— Prescribing Restrictions, 595
— Scopolamine Narcosis, 298, 340, 560
Morphinism, 299
Moss, Sphagnum, 580
Mouth, 463–472
— Excretion in, 468
— Pharmacology, 463–469
— Therapeutics, 469–472
Mouth-wash, 11, 41
Movements, Remedial, 581-582
Mucilage Emulsions, 19
— Suspensions, 17
Mucilago, 6, 9, 141, 142
Muscarine, 332
Mustard, 436
— Volatile Oil of, 437
Myanesin, 324
Myasthenia Gravis, 329, 559
Mydriatics, 577
Myocrisin, 74
Myotics, 577
Myristic Acid, 386
Myristica, 150
Myristicin, 150
Myristin, 150
Myrosin, 436
Myrrha, 153
Myxœdema, 203, 526

NANTWICH WATER, 39
Naphthalene, 428

Naphthol, 427
Narceine, 290, 300
Narcosis Theories, 277
Narcotics, Anodyne, 290–303
Narcotine, 290, 292, 294, 299
Naristillæ, 11
National Formulary, 3
Nativelle's Digitalin, 237
Nauheim Baths, 58, 138, 584
Nebula, 11
Needle Spray, 584
Nembutal, 315
Neoantergan Maleate, 382
Neoarsphenamine, 96, 98, 101
— Administration of, 101
— Biological Tests, 109
— Toxic Effects, 106
— Uses of, 105
Neocaine, 348
Neocinchophen, 376
Neo-epinine, 244
Neo-halarsine, 105
Neokharsivan, 98
Neonal, 315
Neosalvarsan, 98, 101
Neostigmine Bromide, 328
— Methylsulphate, 328
Nepenthe, 300
Nephritis, 566
Nerve Blocking, 343, 347
Nerve Endings, Adrenergic, 241–247, 379
— — Cholinergic, 324–341
— — Drugs acting on, 324, 352, 551–555
— — Parasympathetic, 324–341
— — Sensory, 341–352
— — Sympathetic, 241–247, 379
— — Voluntary Motor, 321–324
Nervous Depressants, Central, 268–320, 551–556
— Stimulants, 260–268, 551–554
— System, 550–561
— — Drugs influencing, 261–352, 550–561
— — Pharmacology, 550–556
— — Therapeutics, 556–561
Neuro-syphilis, 104, 108
Neutral Principles, 6
Neutroflavin, 397
Neutropœnia, 516
Niacin, 192
Nicotinamidum, 192
Nicotine, 320
Nicotinic Acid, 192
Nikethamide, 266
Nitre, 46
Nitric Acid, 128
Nitrite of Amyl, 251
— of Sodium, 253
Nitrites, 251–254
Nitritoid Crisis, 106
Nitrogen Mustard, 218, 513
Nitrogenii Monoxidum, 286
Nitroglycerin, 253
Nitro-Hydrochloric Acid, 130
Nitrous Ether, Spirit of, 253
Nitrous Oxide Gas, 286
— — and Oxygen, 287
Normal Saline, 37, 39
Nostal, 315
Novarsenobenzene, 98, 101
Novocain, 346
Novurit, 94
Nucleotides, 217
Nupercaine, 348
Nutmeg, 150
Nutrient Materials, 187–201
Nux Vomica, 263

Oatmeal, 197
Obesity, 132, 203, 248, 522, 588
Octyl Nitrite, 253
Oculentum, 9
Œstradiol, 219, 220, 221, 222
— Dipropionate, 221, 222, 223
— Monobenzoate, 221, 222, 223
Œstriol, 220, 222
Œstrone, 219, 220, 221, 222
Oil, Empyreumatic, 6
— Fixed, 5
— Volatile, 6, 144–153
Oils, Emulsification of, 18
Ointment, 10
— Compounding of, 24
Olefiant Gas, 288
Oleic Acid, 5, 385, 386
Olein, 384, 387, 390, 393
Oleo-resins, 6
Oleum, 5
— Amygdalæ, 386
— — Volatile, 386
— Anethi, 144
— Anisi, 148
— Arachis, 385
— Aurantii Corticis, 160
— Cadinum, 428
— Cajuputi, 152
— Cari, 148
— Caryophylli, 150
— Chaulmoogræ, 440
— Chenopodii, 183
— Cinnamomi, 151
— Coriandri, 149
— Crotonis, 175
— Cubebæ, 374
— Eucalypti, 434
— Gaultheriæ, 366
— Gossypi Seminis, 386
— Hippoglossi, 188
— Hydnocarpi, 439
— — Æthylicum, 439
— Iodisatum, 124
— Lavandulæ, 152
— Limonis, 161
— Lini, 387
— Menthæ Piperitæ, 147
— Morrhuæ, 196
— Myristicæ, 150
— Olivæ, 384
— Ricini, 166
— Rosmarini, 152
— Santali, 374
— Sesami, 385
— Terebinthinæ, 432
— Theobromatis, 393
Olive Oil, 384
Omnopon, 300
Opium, 290
— Constituents of, 290
— Incompatibles of, 290

Opium, Prescribing of, 595–596
— Pulveratum, 291
— Varieties of, 290
Opsonins, 442
Orange Peel, 160
Organic Acids, 7, 131–133
— Hypnotics, 303–320
Organo Therapy, 201–228, 241–244, 247–251
Organotrop, 100
Orisol, 258
Ortal, 317
Orthocaina, 350
Orthoform, 350
Osteomalacia, 198
Ouabain, 235, 238
Ovarian Cycle, 220
— Hormones, 220–227
Ox Bile, 176
Oxaluria, 522
Oxophenarsine hydrochloride, 99, 104
Oxygen, 135–137, 541, 546
— Mixtures, 135
Oxyhæmoglobin, Drugs decomposing, 513
Oxymel, 9, 143
— Scillæ, 239
Oxytocin, 220, 222, 223, 225, 247–251

PAIN, 556
Palmatine, 158
Palmitic Acid, 5, 384, 386, 391
Palmitin, 384, 385, 387, 390, 393
Paludrine, 360
Pamaquin, 359
Pancreatinum, 162
Pancreatized Food, 163
Pantocaine, 349
Pantopon, 300
Papain, 163
Papaveretum, 300
Papaverine, 290, 294, 300
— Hydrochloride, 301
Papayotin, 163
Para-Aminosalicylic Acid, 411
Paraffin No. 7, 389
Paraffinum Durum, 388
— Liquidum, 166, 388
— — Leve, 388
— Molle Album, 388
— — Flavum, 388
Paraform, 422
Paraldehydum, 303
Paralysis, 558
Paramisan, 411
Parasiticides, 394–431, 575-576
Parasitotrop, 100
Parasympathetic Depressants, 332–341, 555
— Stimulants, 324–332, 554
Parathormone, 205
Parathyroid, 205
— Extract, 205
Paratyphoid Vaccine, 444–445
Paregoric, 291, 435
Parenamps, 213
Parkinsonism, Post-encephalitic, 340, 341
Parmanil, 75
Parrish's Syrup, 81
P.A.S. 411
Pasta, 9
Pastillus, 11, 23
Pathology, 458
Pea-nut Oil, 385
Pearl Coating for Pills, 22
Pectin, 6
Pellagra, 193
Pelletierinæ Tannas, 182
Penicillin, 101, 412–418
— Administration of, 416
— Calcium, 412
— Sodium, 412
— Treatment of Syphilis, 418
Pennyroyal, 377
Pentamethonium, Iodide, 324
Pentamidine Isethionate, 113
Pentaquine Diphosphate, 359
Pentobarbitone Soluble, 315
Pentobarbitonum Sodium, 315
Pentose Nucleotide, 217, 512, 516
Pentothal, 318
Peppermint, 147
Pepsinum, 162
Peptic Ulcer, 483
Peptonized Food, 163
Per-Abrodil, 124
Percaine, 348
Percentage Solutions, 13
Percolation, 8, 10,15
Percussion, 581
Pernæmon, 213
Pernicious Anæmia, 130, 212, 213, 512, 514
Pernocton, 316
Peroxide of Hydrogen, 396, 466
Perspiration, 570
Peru Balsam, 429
— Resinotannol, 429
Peruviol, 429
Pervitin, 247
Pessaries, 11, 23
Pethidine Hydrochloride, 301
Pétrissage, 581
Petroleum, 388
Phanodorm, 316
Phanodorn, 316
Pharmaceutical Chemistry, 1
— Codex, British, 3
— Preparations, 7
— Processes, 14
Pharmacognosy, 1
Pharmacology, 1, 459
Pharmacopœia, British, 2
— Extra, 3
Pharmacy, 1, 14–25
— and Poisons Act, 598
— Practical, 16
Phellandrene, 144, 151, 162
Phemitone, 127, 313
Phenacetinum, 366
Phenadoxone, 302–303
Phenanthrene Alkaloids, 290 ,299
Phenazoni Salicylas, 368
Phenazonum, 367
Phenergan, 383
Pheniodol, 123
Phenobarbitonum, 127, 311
— Sodium, 312
— Solubile, 312

Phenocain, 352
Phenol, 423, 428
Phenolphthaleinum, 172
Phenothiazine, 186
Phenovis, 186
Phenylglycollic Acid, 373
Phenylhydrargyri Nitras, 87, 88
Phenyl Hydrazine Hydrochloride, 217, 512, 515
— Cinchoninic Acid, 376
— Salicylate, 364
Phenytoin, 127, 313
— Soluble, 313
Phenytoinum Sodium, 313
Phloridzin, 505
Pholedrine Sulphate, 247
Phosphoric Acid, 128
Phosphorus, 94
— Radioactive 95, 513, 515
Phthalylsulphathiazole, 409
Physeptone, 302
Physiological Action, 1
Physolactin, 219
Physostigminæ Salicylas, 326
Picraconitine, 438
Picrasmin, 159
Picropodophyllin, 174
Picrotoxin, 268
Pigmentum, 11
— Triplex, 398
Pills, Coating of, 22
— Compounding of, 20–22
— Excipients of, 21
— Finisher of, 22
— Machine for, 21
— Prescribing of, 35
— Varnishing of, 22
Pilocarpinæ Nitras, 330
Pilula, 9, 20
Pinene, 6, 147, 149, 152, 153, 432
Pinol Hydrate, 432
Pitocin, 220, 247–251
Pitressin, 220, 247–251
Pituitary Body Hormones, 218–220, 247–251
Pituitary Posterior Extract, 219, 247-250
Pituitrin, 220, 247
Pix Carbonis Præparata, 428
— Liquida, 428
Placental Extract, 220
Plague Vaccine, 444
Planocaine, 348
Plasmodium Falciparum, 356, 360
— Malariæ, 356
— Vivax, 356, 360
Plasmoquine, 359, 360
Plasters, Compounding of, 25
Plombières, 585
Plumbi Acetas, 68
— Monoxidum, 68
— Subacetas, 68
Pneumonia, 546
Podophylli Resina, 175
Podophylloresin, 174, 175
Podophyllotoxin, 174, 175
Podophyllum, 174
— Indicum, 175
Poisons Act, 598
— — Fourth Schedule, 598
Pollen toxins, 456
Polycythæmia Vera, 515
Polygalic Acid, 258
Pomegranate Bark, 182
Pontocaine, 349
Potassa Caustica, 46
Potassii Acetas, 46
— Bicarbonas, 46
— Bromidum, 125
— Chloras, 46
— Chloridum, 46
— Citras, 46
— Hydroxidum, 46
— Iodidum, 118
— Nitras, 46
— Permanganas, 85
— Tartras, Acidus, 46
Potassium, 45–49
— Antimonyl Tartrate, 109
— Myronate, 436
— Oleate, 387
— Thiocyanate, 254
Poultice, 8, 387, 437
Powders, Compounding of, 19-20
— Prescribing of, 35
Præquine, 359
Pregnancy, Dosage during, 28
Pregneninolone, 225
Preparations, Pharmacopœial, 7–11
Prescribing, 25–36
— of Dangerous Drugs, 595
Prescription Writing, 32–36
Prescriptions in Metric System, 35
Preventive Medicine, 460
Priscol, 254, 539
Procainæ Hydrochloridum, 346
Procaine Borate, 352
Procaine-Penicillin, 415
Proflavine Hemisulphate, 397
Progesterone, 219, 220, 222, 224, 225, 226
Proguanilum Hydrochloridum, 360
Prolactin, 219, 222
Prolan A and B, 218-220, 226, 227
Promanide, 410
Promethazine, 383
Promin, 410
Prominal, 313
Promizole, 410
Prontosil Album, 402
Propamidine Isethionate, 423
Prophylactic, Diphtheria, 449
— Scarlet Fever, 454
— Treatment, 460
Proponal, 314
Propyl-thiouracil, 205
Prostigmin, 328
Protagulin, 455
Protargol, 73
Protectives, External, 384–394, 575, 579
Protein Therapy, 456
Proteins in Diet, 592
— Specific Dynamic Action, 592
— Toxic, 7
Prothrombin, 200
Protopine, 300
Prunase, 155
Prune, Virginian, 154
Prunus Serotina, 154
Prussic Acid, 153, 154
— — Scheele's, 154
Psicaine, 352

Psychotrine, 255
Psyllium Seeds, 166
Pteroylglutamic Acid, 214
Pulmonary Sedatives, 544
Pulverization, 14
— Mediate, 14
Pulvis, 10, 19
— Opii, 291
Punctation, 581
Pungents, 465
Punicine, 182
Pupil, Drugs acting on, 577
Purgatives, 165–176, 489–493, 501–502, 503
— Acting Physically, 165–166
— — on Both Intestines, 173–176
— — on Large Intestine, 167–172
— — on Small Intestine, 166–167
— Anthracene, 167, 492
— Cholagogue, 176–177
— Drastic, 173–176, 492
— Hydragogue, 173, 492
— Hypodermic, 493
— Mercurial, 86, 492
— Mild Irritant, 491
— Saline, 43, 47, 61, 490
Purgen, 172
Pustulants, 573
Pyramidon, 368
Pyranisamine Maleate, 382
Pyrethri Flos, 431
Pyrethrins, 431
Pyrexia, 571
Pyribenzamine, 382
Pyridium, 373
Pyridoxine Hydrochloride, 192
Pyrocatechin, 424
Pyrocatechol, 428
Pyrogallol, 427
Pyroxylinum, 393
Pyruvic Acid, 190

QUASSIA, 159
Quassin, 159
Quebrachine, 578
Quercetin, 174
Quillaia, 259
Quillaiac Acid, 259
Quillaia-Sapotoxin, 259
Quinacrine, 357
Quinalbarbitone Sodium, 316
Quinidinæ Sulphas, 240
Quinidine, 240
Quininæ Bisulphas, 353
— Dihydrochloridum, 353
— et Æthylis Carbonas, 354
— Hydrochloridum, 353
— — Acidum, 353
— Sulphas, 353
Quinine, 353–357, 358, 359, 361
— and Urea Hydrochloride, 361
— and Urethane Injection, 440
— in Malaria, 356
Quinism, 240, 355
Quinophan, 376
Quinoxyl, 361

RABIES ANTITOXIN, 455
Radiant Heat, 589
Radioactivity, 590
Radiography, Iodine Compounds in, 122
Radio-phosphones, 95
Radium, 590
Rational Treatment, 460
Rays, Rœntgen, 589
— Ultra-Violet, 589
Rectal Administration, 27, 495
Red Lotion, 76
Refrigerants, 570
Refrigeration, 138
Regional Anæsthesia, 341–352
Remedies, Combination of, 33
Renal Function Test, 122, 441
Rennet (Rennin), 163
Resene, 433
Resin, 433
Resins, 6
— Suspension of, 18
Resistance Exercises, 582
Resorcinol, 427
— Hexyl-, 373
Respiratory Antiseptics, 545
— Antispasmodics, 543
— Exercises, 545
— Sedatives, 544
— Stimulants, 254–260, 265, 266, 267, 271, 542–549
— System, 540–549
— — Drugs influencing, 254–260, 540–545
— — Pharmacology, 540–545
— — Therapeutics, 545–549
Rhamnetin, 171
Rhatany Root, 179
Rhein, 170, 171
Rheotannic Acid, 170
Rheum, 170
Rheumatoid Arthritis, 217
Rho 1 and 2 (*see* Prolan)
Rhubarb, 170
Riboflavin (Lactoflavin), 191
Ricin, 167
Ricini, Oleum, 166
Ricinoleic Acid, 166, 425
Rickets, 196
Ringer-Lactate Solution, 37, 43, 133, 209
Ringer's Solution, 37
Rochelle Salt, 38
Rœntgen Rays, 589
Roncegno Waters, 85
Rosemary Oil, 152
Rotenone, 430
Roughage in Diet, 501
Roxenol, 425
Rubefacients, 432–440, 573
Ruber, liquor, 140
Rue, 377
Rum, 269
Russell Viper Venom, 455
Rusven, 455

SACCHARINUM, 157
— Sodium, 157
Saccharum Lactis, 155
St. Moritz Waters, 85
Sal Ammoniac, 50
— Volatile, 50
— — Spirit of, 49

Salad Oil, 385
Salicylic Acid, 362
— Ions, 590
Salicylism, 363
Saline Diuretics, 40, 48, 563
— Hypertonic, 39, 40, 41
— Hypotonic, 40
— Normal, 37, 39
— Purgatives, 43, 47, 61, 490
Salipyrin, 368
Salivary Glands, Drugs acting on, 463-466
Salol, 364
— Coating for Pills, 22
Saltpetre, 46
Salts, 594
Salvarsan, 100
— Administration of, 101
Salyrgan, 93
Sandoptal, 315
Sanocrysin, 74
Santali Oleum, 374
Santoninum, 182
Sapo Animalis, 387
— Durus, 387
— Mollis, 387
Saponification, 5, 387
Saponins, 6, 258, 259
— Emulsions, 18
Savin, 377
Scammony Resin, 173
Scarlet Fever Antitoxin, 454
— — Prophylactic, 454
Schick Test Control, 449
— — Toxin, 448
Schizonticides, 356, 358, 359, 360
Schultz-Charlton Test, 454
Schwalbach Waters, 85
Scilla, 239
Scillaren, 239
Scillaridin, 239
Sclerosing Agents, 440
Scopolamine, Drugs containing, 332, 333 339, 341
Scopolamine Hydrobromide, 339
— Morphine Narcosis, 298, 340, 556
Scott's Dressing, 86
Scuroform, 350
Scurvy, 194
Sea-sickness, 486
Seconal, 316
Secretin, 487
Secretions, Internal, 201–228, 241, 247
Secretory disorders, 469
Sedatives, Cerebral, 268–320, 553–556
— Gastric, 474, 476, 483–486
— Intestinal, 187, 493, 498
— Respiratory, 254, 544
Seidlitz Powder, 38, 44
Senega, 258
Senegin, 258
Sennæ Folium, 171
— Fructus, 171
Sensation, Disorders of, 556
Seriparium, 163
Serum, Antidysentericum (Shiga), 454
— Antistreptococcic, 454
— Antivenom, 455
— Desensitization to, 456
— Hæmostatic, 455
Serum, Horse, Normal, 455
— Human Measles, 455
— Sickness, 456
— Therapy, 447–457
Sesame Oil, 385
Sesamin, 386
Sesamol, 386
Sex Hormones, 218–228
Sherry, 269
Shock, Anaphylactic, 106, 456
Sialogogues, 465
Signs and Symbols, 12–13
Silk, Oiled, 580
Silver, 71–74
— Coating of Pills, 22
— Salts of, 71–74
Sinalbin, 436
Sinapis, 436
Sinigrin, 436
Sinusoidal Current, 588
Sippy's Treatment, 61, 483
Skin, Measures affecting, 384–399, 422, 440, 573–576
— Triple Response, 381
Sleep, 556, 560
Smallpox Vaccine, 447
Smelling-salts, 51
Snake Venoms, 455
Soaps, 5, 387
Soda Water, 42, 138
Sodii Benzoas, 369
— Bicarbonas, 37
— Bromidum, 125
— Carbonas, 37
— — Exsiccatus, 37
— Chloridum, 37, 39–41
— Citras, 38, 44
— — Acidus, 45
— et Laurylis Sulphas, 392
— et Potassii Tartras, 38
— Hydroxidum, 37
— Hypophosphis, 95
— Hyposulphis, 115
— Iodidum, 118
— Metabisulphis, 115
— Nitris, 253
— Phosphas, 38
— — Acidus, 39, 45
— — Exsiccatus, 38
— Salicylas, 362
— Sulphas, 38
— — Exsiccatus, 38
— Thiosulphas, 115
Sodium, 37–45
— Antimonyl Tartrate, 110
— Aurothiomalate, 74
— Borate, 395
— Chaulmoograte, 440
— Glycocholate, 176
— Lauryl Sulphate, 392
— Oleate, 387
— Pentose Nucleotide, 217, 512, 516
— Perborate, 396
— Stearate, 387
— Stibogluconate, 112
— Taurocholate, 176
— Thiosulphate, 115
Solantoin, 313
Solganal, 75
Soluble Fluorescein, 440

Soluble Sulphacetamide, 403
— Sulphadiazine, 405
— Sulphamerazine, 408
— Sulphathiazole, 404
Solution, 9, 15
— Percentage, 13
Solvellæ, 11
Solvent Ether, 283
Solvents for Tinctures, 10
Somnosal, 368
Soneryl, 315
Spa Waters, 85
Sparteine, 321
Spas, 584–587
Sperm Oils, 391
Spermaceti, 391
Sphagnum Moss, 580
Spinocaine, 348
Spirit, Mindererus', 50
Spirit of Sal Volatile, 49
Spiritus, 10
— Frumenti, 269
— Methylatus, 269
— Rectificatus, 269
Spongio-Piline, 580
Squill, 239
Stabilarsan, 109
Standardization of Drugs, 8, 10
Staphylococcus Toxoid, 452
— Vaccine, 444
Starch, 393
Stearic Acid, 5, 386, 391
— — Coating for Pills, 22
Stearin, 385–387, 390, 393
Stearoptenes, 6, 144
Sterilization, 15
Stibophen, 111
Stilbamidine Isethionate, 113
Stilbenes, 221
Stilbœstrol, 221
Stimulants, Cardiac, 228–241, 244, 529–539
— Cerebral, 260–268, 552–554
— Circulatory, 228–254, 529–539
— Cutaneous, 432–440, 573–576
— Gastric, 158–162
— Gustatory, 464, 473
— Hepatic, 505
— Intestinal, 165–176, 489–493
— Motor, 553
— Nervous, 551–554
— Renal, 563–565
— Respiratory, 139, 254–260, 261, 265, 266, 267, 271, 542–549
— Sensory, 551
— Uterine, 218–228, 247, 377–380, 578
Stockholm Tar, 428
Stomach, 473–486
— Hog's, 215
— Pharmacology, 473–479
— Therapeutics, 480–486
Stomachics, 158–162, 473
Storax, 429
Stovaine, 352
Stovarsol, 108
Straining, 15
Stramonium, 341
Strathpeffer Waters, 115
Streptocide, 402
Streptococcus Toxin, 454
Streptomycin, 418
— Treatment of T.B., 419
— Toxic Effects, 420
Stroking, 580
Strophanthin, 238
Strophanthus, 238
Strychnina, 263
Strychninæ Hydrochloridum, 263
Strychnine Poisoning, 264
Stupes, Turpentine, 433
Styptic Wool, 579
Styptics, 516
Stypven, 455
Styracin, 429
Styrax Præparatus, 429
Styrol, 429
Subcutaneous Injection, 9, 26, 35
Sublimation, 15
Subscription, 33
Succinylsulphathiazole, 409
Sucrosum, 155
Sudorifics, 331, 570
Sugar, 155
— Coating for Pills, 22
Sulphacetamide, 403
— Sodium, 403
Sulphadiazine, 405, 547
— Sodium, 405
Sulphadimidine, 406, 547
— Sodium, 407
Sulphaguanidine, 408
Sulphamerazine, 407, 547
— Sodium, 408
Sulphamethazine, 406
Sulphanilamide, 402
Sulphapyridine, 408
Sulpharseno-benzene, 99, 105
Sulpharsenol, 99, 105
Sulpharsphenamine, 99, 105
Sulphasuxidine, 409
Sulphathiazole, 404, 547
— Sodium, 404
Sulphetrone, 410
Sulphonal, 308
Sulphonamides, 399–410
— Toxic Effects, 401
Sulphone Hypnotics, 308–309
Sulphones, 410–412
Sulphur, 113
— Flowers of, 113
— Milk of, 113
— Præcipitatum, 113
— Sublimatum, 113
— Waters, 115
Sulphuretted Hydrogen, 114
Sulphuric Acid, 129
Suppositoria, 10, 23, 496
Suppositories, Compounding of, 23
— Prescribing of, 35
— Uses of, 496
Suprarenal Cortex, 216
Suramin, 112
Suspension of Insoluble Salts, 17
— of Oils, 18
— of Resins, 18
Sweat, Drugs influencing, 570–572
Sweetening Agents, 155–157, 465
Symbols and Signs, 12–13
Sympathetic Depressants, 379
— Stimulants, 241, 245, 246, 378, 554

Symptomatic Treatment, 461
Syncurine, 323
Synergism, 29
Synkavit, 199
Syphilis, Arsenical Treatment of, 101
— Bismuth Therapy, 67
— Iodine in, 121
— Mercury Treatment of, 92
— Penicillin Treatment of, 418
Syrup of Figs, 172
Syrupus, 10, 155

T.A.B. VACCINE, 444
Tabellæ, 10
Tables of Equivalent Doses, 36
Tablet Triturates, 22
Tablets, Compressed, 22
Tachycardia, 537
Talc, 60, 350, 394, 395
Tannic Acid, 177, 180
— — Astringents, 177–181
— — Paste, 177
Tapotement, 581
Tar, 428
Tartar, Cream of, 46
— Emetic, 109
Tartaric Acid, 131
Taste Buds, Drugs stimulating, 464
Taurocholate, Sodium, 176
Tea, 260
— Beef, 595
T.E.A.B., 254
Teeth, Drugs influencing Calcification, 463
Temperature, Drugs influencing, 352–369
T.E.P.P., 329
Terebinthinæ Oleum, 432
Terpenes, 6, 150
Terpinene, 162
Terpineol, 149, 152, 153, 426
Testicular Hormone, 227
Testosterone, 227
— Proprionate, 227
Tetanus Antitoxin, 451
— Toxoid, 451
Tetany, 57, 198, 205
Tetracaine, 349
Tetrachlorethylene, 184
Tetræthyl-Ammonium bromide, 254
Tetraethyl pyrophosphate, 329
Tetramethylthionine Chloride, 441
Thalazole, 409
Thalleioquin Reaction, 353
Thallium Acetate, 71
Theamin, 372
Thebaine, 290, 292, 299
Theine, 260
Theobroma, Oil of, 393
Theobrominæ et Sodii Salicylas, 370
Theocine, 371
Theophyllina, 370
— et Sodii Acetas, 371
Theophylline Ethylene-diamine, 371
— Monoethanolamine, 372
Therapeutics, Definition of, 2
— Foundations of, 458
— Rational, 460
Thermogene Wool, 579
Thermogenetic Centre, 569
— — Drugs acting on, 352–369, 571
Thialpentone, 320
Thiamine Hydrochloride, 190
Thiazamide, 404
Thiocyanate, Potassium, 254
Thioparamizone, 412
Thiopentone Sodium, 318
Thiosemicarbazones, 412
Thiosulphate, Sodium, 115
Thiouracil, 203
Thrombin, Human, 456
Thromboplastin, 456
Thrombosis, 538
Thymol, 185
Thyroideum, 201
Thyroidism, 202
Thyrotoxicosis, 526
Thyrotropic Hormone, 219
Thyroxine, 201, 202
Tinctura, 10
— Ammoniata, 10
— Composita, 10
— Standardized, 10
Tobacco, 320
Tocopherol, 199
Tocopheryl Acetate, 199
Tolerance, 30
Tolu Balsam, 259
Toluene, 428
Tolu-resinotannol, 260
Tonics, Cardiac, 228–241, 529–539
— Hæmatinic, 511–516
— Stomachic, 473–477
Tonsillitis, 471
Toothache, 470
Totaquina, 354, 357
Tow, 580
Toxalbumoses, 7, 167, 176
Toxinum Diphthericum Calefactum, 449
— — Detoxicatum, 449
— — Diagnosticum, 448
— Staphylococcicum Detoxicatum, 452
— Tetanicum Detoxicatum, 451
Toxoid, 449
— Antitoxin Floccules, 450
— — Mixture, 449
Tragacantha, 141
Tragacanthin, 142
Transmission, Intestinal, 489
Treatment, 458–462
— Ætiological, 458, 461
— Antiseptic, 394, 466
— Dietetic, 591–595
— Electrical, 587–590
— Empirical, 461
— Exercises, 580–582
— Expectant, 461
— Heat, 583, 588, 589
— Ionic, 590
— Light, 589
— Massage, 580–581
— Palliative, 461
— Preventive, 460
— Prophylactic, 460
— Radium, 590
— Rational, 458
— Remedial, 460
— Specific, 461
— Sunlight, 590

Treatment, Symptomatic, 461
— Ultra-Violet Rays, 589
— X-Ray, 589
Trefriw Waters, 85
Tribromoethyl Alcohol, 304
Trichloracetic Acid, 132
Trichloroethylene, 289
Tridione, 313
Trigemin, 368
Trigonelline, 238
Trikresol, 425
Trilene, 289
Trimethylene, 288
Trinitrin, 253
Trional, 309
Tripellinamide, 382
Triple Dye, 186, 398
Triturates, Tablet, 22
Trituration, 14
Trochiscus, 10
Tropacocaine Hydrochloride, 351
Tropic Acid, 333
Tropine, 333, 338
Troxidone, 313
Tryparsamidum, 107, 108
Trypsin, 162
Tubercle Vaccines, 446
Tuberculin, Old, 446
— Protein Derivative, 446
— P.P.D., 446
Tuberculinum Pristinum, 446
Tuberculosis, Pulmonary, 548
Tubocurarine Chloride, 321
Turpentine, 377, 432
Turpethum, 174
Tutocaine, 352
Twilight Sleep, 298, 340, 556
Typhoid and Paratyphoid Vaccine, 444
Typhus Vaccine, 445
Tyramine, 377

ULCER, GASTRIC, 42
Ultra-Violet Rays, 589
Unguentum, 10, 24
Unna's Paste, 75
Uradal, 310
Uræmia, 567
Urea, 372
— Concentration Test, 372
— Excretion, 505
— Hypnotics, 309–310
— Stibamide, 112
Urethanum, 309
Uric Acid Diathesis, Drugs influencing, 521, 525, 564, 567
— — Excretion, 376, 521
Urinary Antiseptics, 45, 372–374, 565, 568
— System, Drugs acting on, 369–376, 562–568
Uropac, 123
Uroselectan, 123
Urotropine, 372
Uterus, Drugs acting on, 218–228, 247 355, 377–380

VACCINES, 441–447
— Actions of, 442
Vaccines, Autogenous, 443
— Bacterial, 443
— Flexner, 444
— Hay-fever, 456
— Polyvalent, 443
— Preparation of, 441
— Stock, 443
— T.A.B., 444
Vaccinum Acnes, 443
— Choleraicum, 443
— Dysentericum, 444
— Febris Flavæ, 445
— Pertussis, 444
— Pestis, 444
— Staphylococcicum, 444
— Tuberculinum, 446
— Typhi Exanthematici, 445
— Typho-paratyphosum, 444
— Vacciniæ, 447
Valeriana, 152
Valerianic Acid, 153
— Aldehyde, 152
Valeric Acid, 153
Valvular Disease, 534
Vanillin, 429
Vapor, 11, 26
Vapour Baths, 583
Varicose Veins, 440, 539
Varnishing of Pills, 22
Vaseline, 388
Vaso-constrictors, 241–250, 532
Vaso-dilators, 251–254, 532
Vasopressin, 220, 247, 248, 249, 250
— Tannate, 248, 250
Veganin, 366
Vegetables in Diet, 593
Vehicle, 34
Veins, Drugs affecting, 529
— Sclerosing Solutions, 539
Venesection, 529, 533
Venom, Russell Viper, 455
Venous Pressure, Reduction of, 234, 533, 535
Ventriculin, 215
Veramon, 368
Veratrine, 554
Veritol, 247
Vermicides, 181–186, 495
Vermifuges, 181–186, 495
Veronal, 310
Vesicants, 437, 573
Vessels, Drugs acting on, 241–254, 531 538
Vibration, 581
Vichy Waters, 42, 49
Vienna Paste, 54
Vinegar, 7
Vinesthene, 285
Vini Gallici, Spiritus, 269
Vinyl Ether, 285
Viola Crystallina, 186, 398
Virginian Prune Bark, 154
Viride Nitens, 399
Vitamin A, 188–189, 198, 380, 525
Vitamin B, 190–193
Vitamin B_{12}, 215
Vitamin C, 193–195
Vitamin D, 56, 57, 195–199, 510, 525
Vitamin E, 199
Vitamin K, 199, 510, 516, 525

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